Interim Session — Philadelphia
December 2-3, 1957

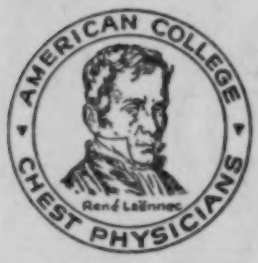
VOLUME XXXII NUMBER 1

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



PUBLISHED MONTHLY

JULY
1957

PUBLICATION OFFICE, CHICAGO, ILLINOIS
EXECUTIVE OFFICE, 112 EAST CHESTNUT STREET, CHICAGO 11, ILLINOIS

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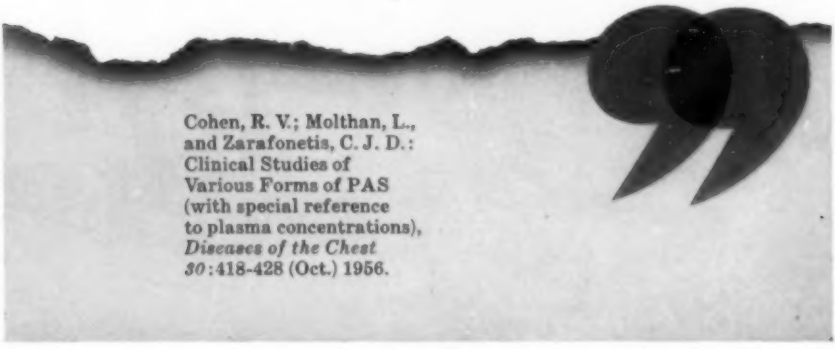

Cohen, R. V.; Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations), *Diseases of the Chest* *30*:418-428 (Oct.) 1956.

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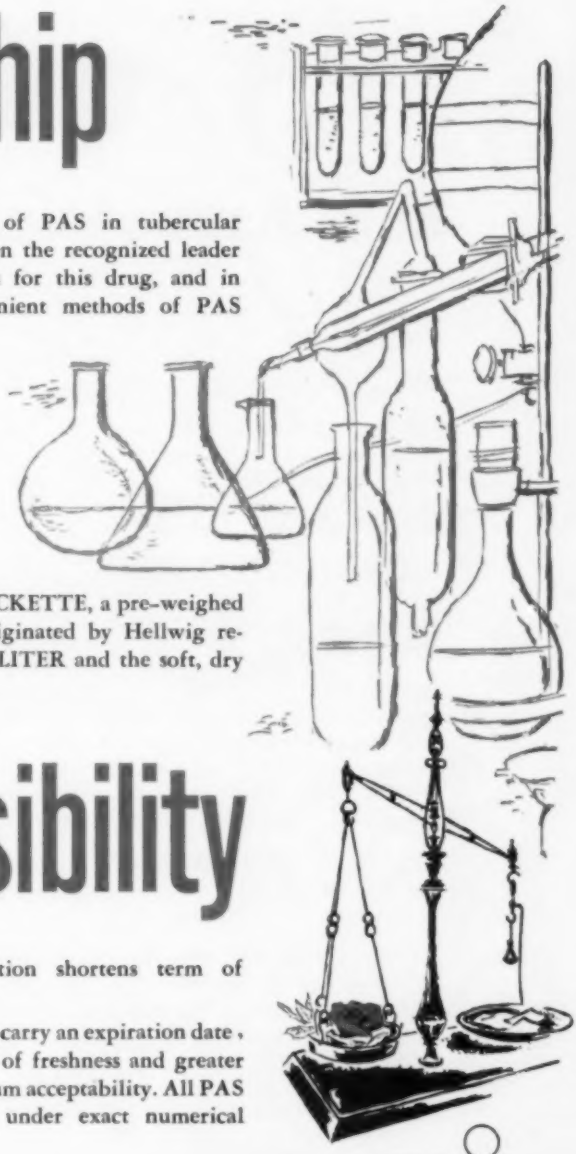

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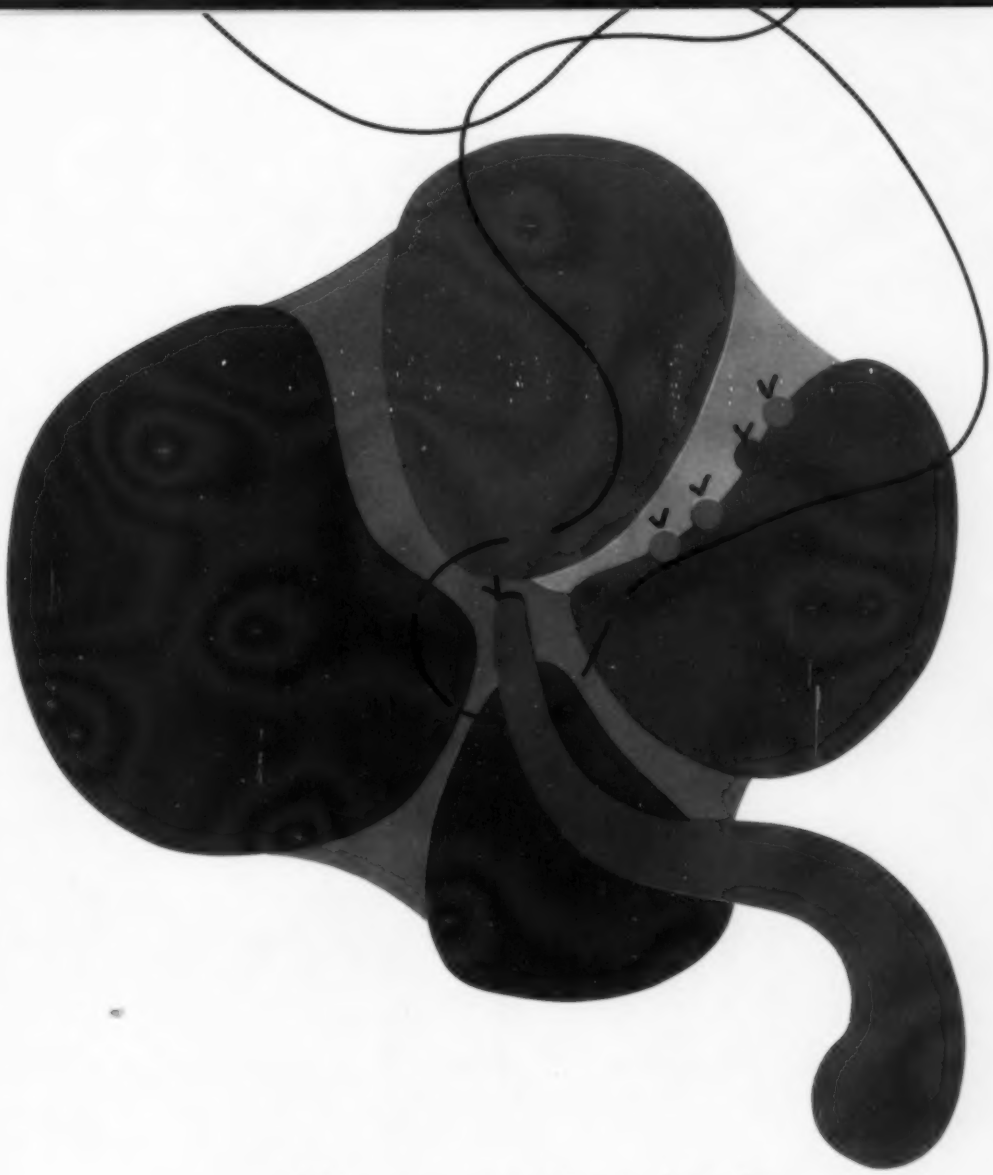

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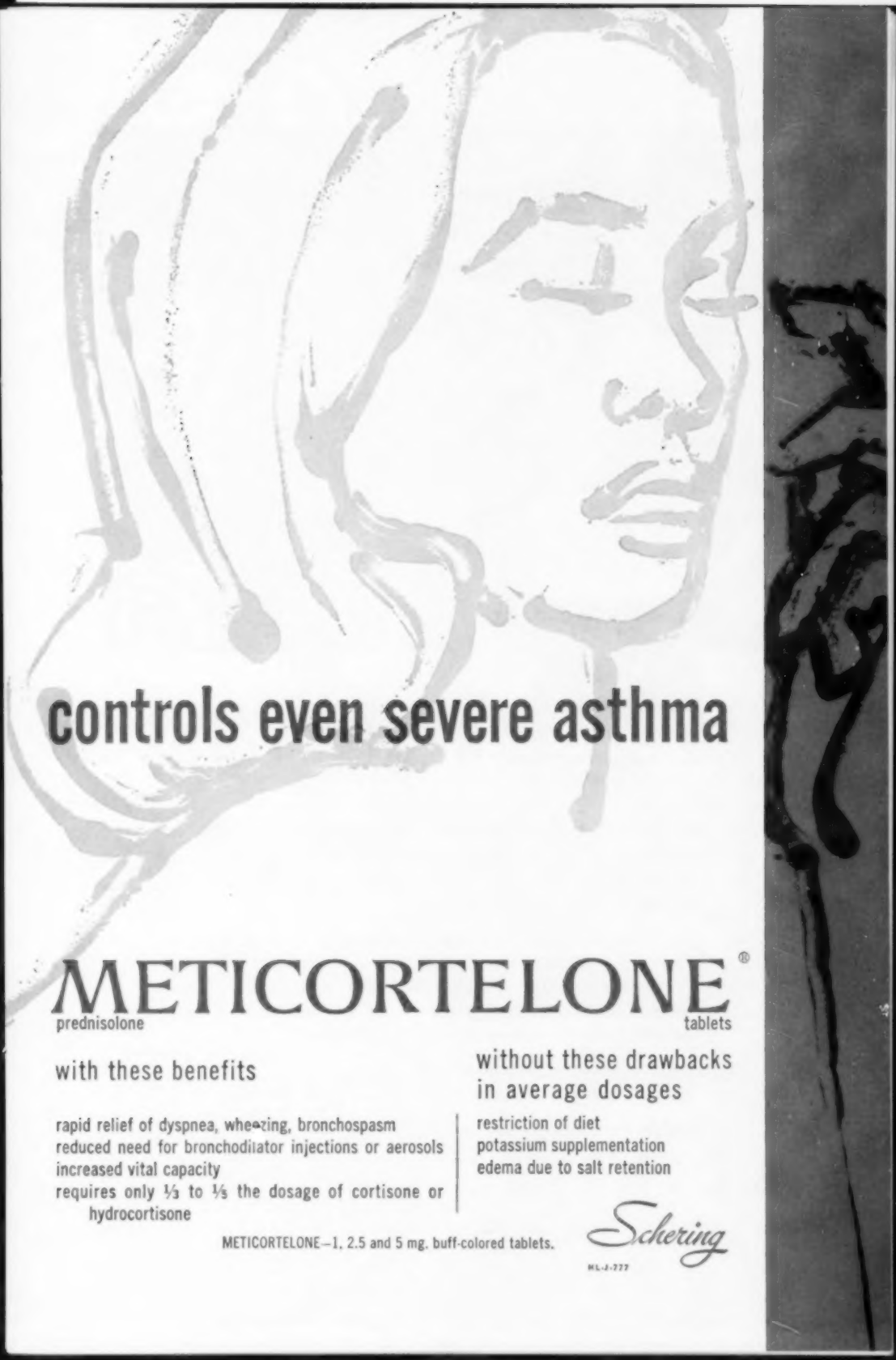

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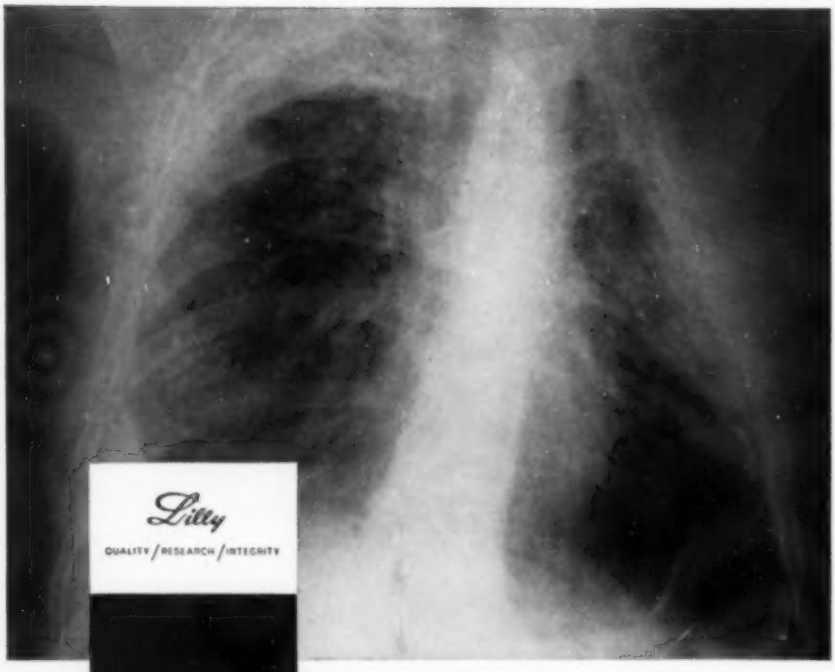

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DISEASES of the CHEST

VOLUME XXXII JULY, 1957 NUMBER 1

The Cardiorespiratory Syndrome of Obesity

GLEN A. LILLINGTON, M.D.,* MILTON W. ANDERSON, M.D., F.C.C.P.** and ROBERT O. BRANDENBURG, M.D.**

Rochester, Minnesota

The association between obesity, impaired respiratory function and polycythemia has recently aroused considerable speculation and investigation. While it has long been known that the hypoxemia present in certain pulmonary and cardio-vascular diseases may lead to secondary polycythemia, it is now postulated that marked obesity per se, in the absence of intrinsic pulmonary disease, may compromise respiratory function to such an extent that secondary polycythemia ensues.

The reduced vital capacity in obesity has been described by many workers.[1-3] In 1936, Kerr and Lagen[4] reported a series of patients with obesity, plethoric facies and cyanosis, reduced vital capacity, polycythemia and, in some cases, the development of congestive heart failure. They postulated that obesity gave rise to "postural emphysema" which led to alveolar hypoventilation, arterial hypoxemia and secondary polycythemia, and stated that loss of weight was accompanied by reversal of the syndrome. A high incidence of polycythemia in obese persons was reported by Báez Villaseñor and associates[5] in 1951 and more recently by Weil,[6] who ascribed the polycythemic state in his cases to ventilatory impairment secondary to obesity. In Lawrence and Berlin's[7] study of the "polycythemia of stress," obesity was present in eight of 18 cases. Boyer and Bailey[8] noted an elevated carbon dioxide tension in expired gas of obese persons. The triad of obesity, alveolar hypoventilation with hypoxemia and secondary polycythemia, in the absence of intrinsic pulmonary disease, has been further described in several recent reports.[9-15]

Although it is generally agreed that arterial oxygen saturation is normal in polycythemia vera,[16, 17] this has been questioned in two recent papers. Newman and co-workers[18] performed detailed studies of pulmonary function in five patients whose condition had been diagnosed as polycythemia vera. Two of these patients, both very obese, exhibited hypoxemia, hypercapnia and considerable impairment in ventilatory function. It would appear likely that the polycythemia in these two cases is secondary rather than primary. Ratto and associates[19] reported the presence of alveolar

*Fellow in Medicine, Mayo Foundation.

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The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

TABLE I

RESULTS OF TESTS OF PULMONARY FUNCTION IN SEVEN OBESE PATIENTS*

Date of test		Case 1 (M, 44 yr., 336 lb., 71 in.) Dec. 5, 1951	Case 2 (M, 46 yr., 222 lb., 69 in.) Jan. 5, 1952		Case 3 (F, 28 yr., 400+ lb., 62 in., later 248 lb.) Mar. 21, 1955-Oct. 4, 1955	Case 4 (M, 40 yr., 364 lb., 70 in.) July 26, 1951	Case 6 (M, 48 yr., 196 lb., 68 in.) Aug. 12, 1955	Case 7 (M, 46 yr., 258 lb., 69 in.) Aug. 22, 1953	Case 8 (M, 66 yr., 276 lb., 67 in.) Aug. 14, 1956
Vital capacity (liters)		3.54 (68)	4.24 (88)	....	3.98 (128)	3.43 (65)	2.71 (59)	2.04 (43)	2.87 (64)
Residual volume (liters)		....	....	....	0.96 (80)	....	2.54 (169)	2.49 (156)	2.47 (165)
Total capacity (liters)		....	....	....	4.93 (115)	....	5.24 (86)	4.53 (71)	5.34 (89)
Residual volume / Total volume X 100 (per cent)		....	....	....	19	....	48	55	46
Functional residual capacity (liters)		....	....	....	2.13 (112)	....	3.37 (125)	2.88 (99)	3.06 (113)
Inspiratory capacity (liters)		3.5 (92)	3.1 (89)	....	2.87 (120)	3.03 (78)	2.06 (61)	1.62 (46)	2.09 (63)
Expiratory reserve (liters)		0.08 (6)	1.14 (87)	....	1.18 (169)	0.40 (29)	0.83 (69)	0.39 (30)	0.59 (49)
Maximal breathing capacity (liters per minute)		....	....	....	98 (81)	....	45 (36)	35 (24)	49 (40)
Expiratory slowing† (grade)		....	....	....	0	....	2	3	0-1
Nitrogen washout index‡ (per cent)		....	....	....	0.9	....	5.9	5.5	0.9
Arterial oxygen saturation (per cent); breathing room air§	Rest	87-94	86-96	70-90	95-98	97-98	84-87	85-90	96-97
	Exercise	91	93	....	98	95	80	81	93
	Duration of exercise	5 min.	1.5 min.	....	2.9 min.	2 min.	1.7 min.	1.7 min.	3.5 min.
Arterial oxygen saturation (per cent); breathing 100 per cent oxygen		100	100	100	100	100	100	100	100

*All volumes are expressed as liters or liters per minute BTPS.

Figures in parentheses indicate percentage of predicted normal values derived from the formulae of Bateman.[20]

†Measured by the maximal midexpiratory flow method of Leuallen and Fowler[21] and graded 0 to 4.

‡Normal value is < 2.5 per cent.

§Normal value is 95 to 98 per cent.

hypoventilation, hypoxemia and polycythemia in a "large man" with normal lung volumes and normal maximal breathing capacity. They attributed the alveolar hypoventilation to depressed sensitivity of the respiratory center, the cause of which was undetermined.

From these studies has arisen the concept of a clinical syndrome characterized by extreme obesity, cyanosis, breathing irregularities, congestive heart failure and a tendency toward excessive lethargy and somnolence. Laboratory studies reveal absolute polycythemia, pulmonary hypertension,[10, 12] arterial hypoxemia and hypercapnia, compensated respiratory acidosis, alveolar hypoventilation and certain abnormalities in the ventilatory tests of pulmonary function. Definitive evidence of primary pulmonary disease or a right-to-left cardiovascular shunt is lacking. Appropriate reduction in weight appears to reverse the clinical and laboratory signs of the syndrome.

Although obesity is now considered to be the primary factor in the development of this syndrome, the exact mechanism by which the excessive weight leads to hypoxemia and hypercapnia is not entirely clear. In an effort to clarify this problem and to document further the occasional occurrence of this interesting disease entity, the clinical records of a series of extremely obese patients seen at the Mayo Clinic were reviewed. Only patients on whom arterial oxygen saturation studies had been made were included in the series.

Eight cases were selected for presentation: Four obese patients had polycythemia and were free from evidence of intrinsic pulmonary or cardiac disease; three obese patients with secondary polycythemia had definite bronchopulmonary disease of some form, but obesity was considered to play a significant role in the genesis of the arterial hypoxemia; one patient had obesity without polycythemia but displayed arterial oxygen desaturation on exercise.

Report of Cases

Case 1: A 44 year old man came to the clinic in November, 1951, complaining of moderately severe exertional dyspnea, without orthopnea, of several years' duration and of cyanosis of the face and lips for the previous year. The cyanosis was said to be more marked when he was asleep. He had noticed excessive drowsiness and some edema of the ankles for 6 months. He had been told in 1949 that his blood pressure was elevated, and he had weighed more than 300 pounds for several years.

His height was 71 inches and his weight was 370 pounds. He had ruddy cyanosis which was more marked on recumbency. There was minimal edema of the legs but abnormalities of the heart or lungs were not noted. Funduscopic examination revealed congestive retinal veins. Blood pressure was 185 mm. of mercury systolic and 120 mm. diastolic. It was noted that his breathing was very shallow.

A roentgenogram of the thorax showed minimal linear fibrosis in the lower left lung. Tests showed the presence of albuminuria, grade 2, and casts in the urine sediment. The concentration of hemoglobin was 16.4 gm. per 100 cc. of blood; the hematocrit reading was 60 per cent; erythrocytes numbered 5,790,000 and leukocytes 5,600 per cubic millimeter of blood, and the differential blood count was normal. Carbon dioxide combining power measured 29 mEq. and serum chlorides 88.8 mEq. per liter. The value for urea was 21 mg. and for fasting blood sugar, 115 mg. per 100 cc. of blood. The values for serum calcium, cholesterol, proteins, potassium and sodium were normal, and measurements of urinary excretion of 17-ketosteroids and corticoid gave normal results. The electrocardiogram (Fig. 1) disclosed an R-R' configuration in lead V_1, prominent S waves in leads I, aVL, and V_6, a late R deflection in lead aVR, prominent P waves in leads I and II, a normal electric axis and

inverted T waves from leads V_1 to V_6. The interpretation was that of right ventricular overload.

Treatment consisted of reduction of weight (600 calorie diet) and removal of 1,000 cc. of blood by phlebotomies. Studies of pulmonary function were carried out 2 weeks after his admission, at which time he weighed 336 pounds (Table I). The vital capacity and expiratory reserve volumes were significantly reduced.* There was no spirographic evidence of expiratory obstruction, but the tidal volumes were low (less than 200 cc.) and the tracing showed apneic periods. Arterial oxygen saturation (determined by ear oximetry with the double scale oximeter[22]) with the patient breathing room air was 87 to 94 per cent when he was at rest and 91 per cent on exercise (stepping up and down from a 9-inch step 15 times per minute for 5 minutes), but increased to 100 per cent when he breathed pure oxygen.

*All values for lung volumes, minute ventilation, and maximal breathing capacity are expressed as liters or liters per minute BTPS.

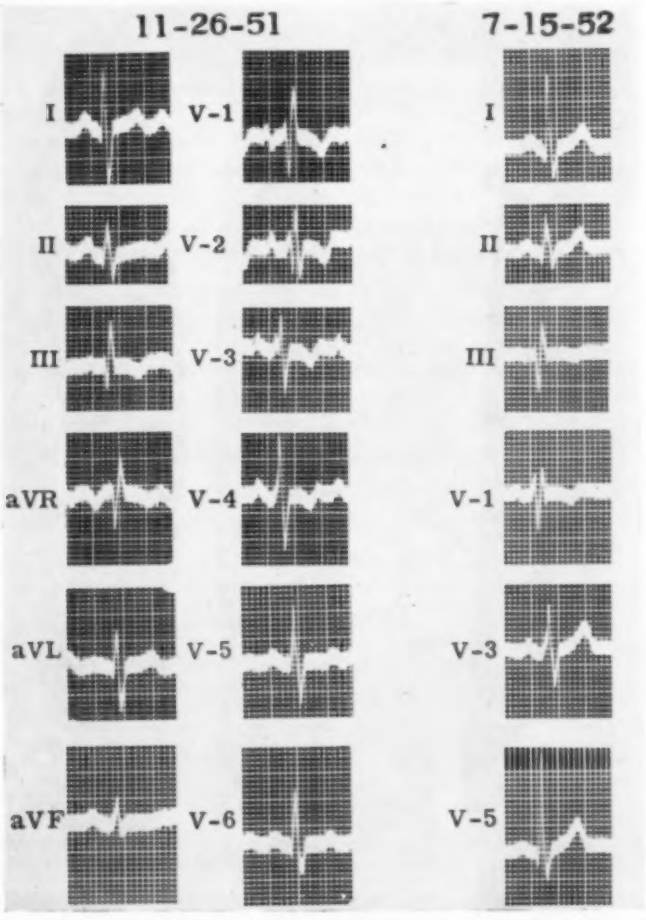

FIGURE 1: Electrocardiograms for a 44 year old man (Case 1). Note the changed electric axis, decreased height of P waves in the standard leads, elevation of T waves in the right precordial leads and the decreased amplitude of the S wave in V_5 after a loss of 70 pounds.

Arterial blood samples, obtained in all cases by needle puncture of the radial artery, were studied 2 days later (Table II). On breathing air, arterial desaturation and an elevated $P_{a}co_{2}$ (partial pressure of carbon dioxide in arterial blood expressed in millimeters of mercury) were noted. On breathing pure oxygen, the saturation increased to 100 per cent but the $P_{a}co_{2}$ increased from 55 to 70 mm. and the pH decreased from 7.36 to 7.25. This was interpreted as partially compensated respiratory acidosis which was aggravated by a further decrease in ventilation on breathing oxygen. Arterial dye-dilution curves, measured by continuous ear oximetry after injection of Evans blue dye into a peripheral or central vein, did not show evidence of shunts but the circulation time was somewhat prolonged. Continuous oximetry while the patient breathed room air showed remarkable changes in oxygen saturation of arterial blood with each respiration; saturation decreased when the breath was held in expiration and increased to normal range on voluntary hyperventilation. These fluctuations were abolished by breathing 100 per cent oxygen.

At the time of his dismissal a week later, the patient weighed 329 pounds. Final diagnosis was arterial hypoxemia with secondary polycythemia due to mechanical restriction of ventilation by obesity.

He returned to the clinic in August, 1952, weighing 300 pounds. He stated that he stayed awake more easily and had less dyspnea and no pedal edema. On examination, his blood pressure was 140/90 and cyanosis was absent. The urine did not contain albumin, the concentration of hemoglobin was 15.4 gm. per 100 cc. of blood, and erythrocytes numbered 4,630,000 and leukocytes 6,300 per cubic millimeter of blood. The hematocrit reading was 52 per cent and serum chlorides measured 99.4 mEq. per liter. The electrocardiogram (Fig. 1) showed smaller P waves and some left axis deviation. The R′ in lead V_1 and the S in leads I and V_5 were smaller.

Case 2: A 46 year old farmer was brought to the clinic in a semicomatose condition in December, 1951. He had been grossly overweight for many years "due to an uncontrollable appetite" and had recently weighed 273 pounds. Plethora and excessive drowsiness had been present for 9 years, and his condition had been diagnosed as narcolepsy. Dyspnea occurred on minimal exertion and he became cyanotic on coughing or lying down.

On the patient's admission, the oral temperature was 101° F. He was restless, somewhat disoriented and confused, and fell asleep repeatedly. He was plethoric and deeply cyanotic. His respirations were irregular, shallow and rapid, with recurrent episodes of apnea resembling Cheyne-Stokes breathing. He had a dry nonproductive cough. Peripheral venous distension and edema were not noted; the heart tones were normal, but coarse rales were heard over the right lung. Blood pressure was 160/90 and funduscopic examination showed dark, dilated retinal veins.

The concentration of hemoglobin was 19.0 gm. per 100 cc. of blood; the hematocrit reading was 72 per cent. Erythrocytes numbered 7,120,000 per cubic millimeter of blood, but the platelet, leukocyte and differential counts were normal. Albuminuria, grade 3, was present as well as microscopic hematuria, the latter being attributed to the indwelling catheter. The carbon dioxide combining power was 39.4 mEq. and the value for chlorides was 93.6 mEq. per liter. The values for blood sugar, blood urea, serum sodium and potassium were within normal limits. A roentgenogram of the thorax showed a questionable density in the left costophrenic angle. The electrocardiogram (Fig. 2) showed right axis deviation, high peaked P waves in leads II and III, a W-shaped QRS in V_1, a deep S wave in V_5, and shallow inverted T waves in V_2 and V_5.

Penicillin was given intramuscularly and the patient was placed in an oxygen tent, which relieved his cyanosis but seemed to make him sleepier. Daily for 6 consecutive days 500 ml. of blood was removed by phlebotomy. His temperature became normal; he appeared more alert the day after admission, and was taken from the oxygen tent 2 days subsequently. A roentgenogram of the thorax on the fourth day of hospitalization showed clear lung fields and slight enlargement of the cardiac silhouette. An electro-encephalogram and a determination of 17-ketosteroids excreted in the urine were within normal limits.

Studies of pulmonary function were made on the tenth hospital day, at which time he was alert and greatly improved clinically with a relatively normal breathing pattern. He weighed 222 pounds and his height was 69 inches. Ventilatory studies gave essentially normal results (Table I). Although the arterial oxygen saturation when the patient was at rest was 86 per cent initially, it later increased to 96 per cent but decreased to 93 per cent after 1.5 minutes of exercise. The saturation increased to 100 per cent when pure oxygen was breathed. Arterial blood studies 3 days later showed a radial pressure of 122/58 and an oxygen saturation of 96 per cent when room air was breathed and 100 per cent when oxygen was breathed. Arterial dye-dilution studies showed a normal circulation time and no evidence of shunts.

Before his dismissal from the hospital, the patient was given 6.5 mc. of radiophosphorus. He weighed 220 pounds on dismissal and the hematocrit reading was 50

per cent. The diagnosis was considered to be polycythemia vera at that time.

He returned to the clinic in November, 1952, complaining of dyspnea and excessive somnolence as before. He weighed 225 pounds; blood pressure was 140/80 and musical rales could be heard over both lungs. Albuminuria, grade 2, was noted; the concentration of hemoglobin measured 17.6 gm. per 100 cc. of blood; erythrocytes numbered 5,800,000 and the hematocrit reading was 62 per cent. Platelets and leukocytes were normal in all respects. The total blood volume* was 8,358 cc. and the plasma volume was 3,176 cc. A roentgenogram of the thorax did not show evidence of abnormality. Phlebotomy of 500 ml. of blood was performed, another 4 mc. of radiophosphorus was administered, and he was advised to lose weight.

He returned to the clinic in June, 1954, complaining of increased dyspnea and sleepiness. He had had repeated phlebotomies by his home physician. His weight had increased to 242 pounds and moist rales and wheezes were heard over both lungs. Albuminuria, grade 2, was present. The concentration of hemoglobin was 12.6 gm. per 100 cc. of blood; erythrocytes numbered 5,890,000 and the hematocrit reading was 52 per cent. Leukocyte and platelet counts were normal and the sternal bone marrow was reported to be "moderately hypocellular." The electrocardiogram appeared

*All blood volumes were determined by the Congo red dye-dilution technic.

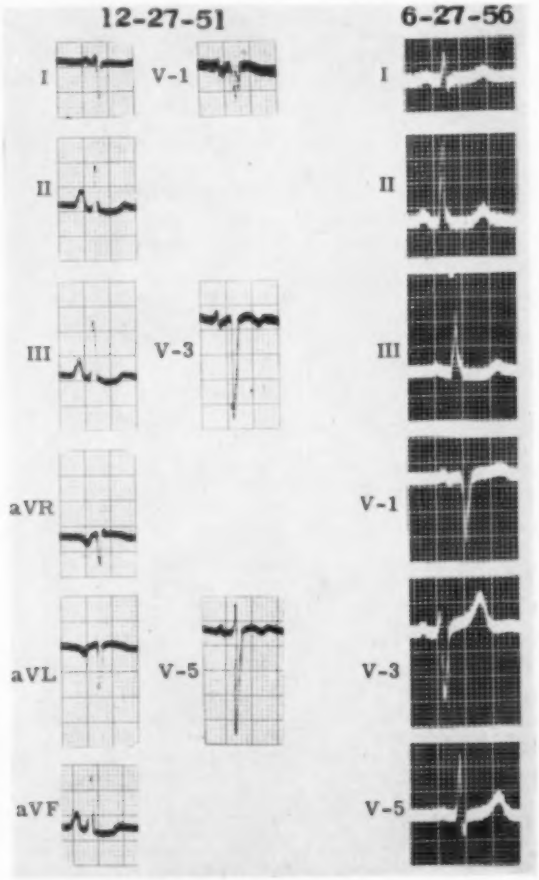

FIGURE 2: Electrocardiograms for a 46 year old man (Case 2) before and after a loss of 80 pounds.

unchanged from the one made in 1951, but a roentgenogram of the thorax revealed some cloudiness at the base of the right lung and slight cardiac enlargement. A similar roentgenogram made a week later showed considerable clearing. Two specimens of sputum failed to show acid-fast bacilli on bacteriologic examination or abnormal cells on cytologic examination. He was again advised to lose weight.

The patient returned to the clinic in December, 1954, with complaints of dyspnea and orthopnea of sufficient severity to incapacitate him completely. He had had 12 phlebotomies in the previous 6 months and had been given digitalis. His weight was 250 pounds and the blood pressure was 140/78. He was plethoric and cyanotic. Congestive heart failure was not evident, but rales were heard at the bases of both lungs on inspiration and expiration. Urinary and hematologic findings were essentially unchanged, and a roentgenogram of the thorax showed slight cardiac enlargement with pulmonary congestion, mostly at the base of the right lung. The patient was given a rigid reduction diet of 800 calories.

He followed the diet faithfully and by August, 1955, had reduced to 166 pounds. He reported that he felt very well and was able to perform full-time farm labor. Somnolence, cyanosis and dyspnea had disappeared; phlebotomy had not been required and he had not had to take digitalis.

He reported to the clinic again in June, 1956. Although his weight was up to 190 pounds, he had no symptoms except for some cough and expectoration which he attributed to smoking. Blood pressure was 120/80 and the lungs were normal on physical examination. The concentration of hemoglobin was 15.4 gm. per 100 cc. of blood; erythrocytes numbered 5,390,000 per 100 cc. of blood, and the hematocrit reading was 53 per cent. Albumin was not present in the urine and the blood urea measured 26 mg. per 100 cc. The electrocardiogram (Fig. 2) showed striking improvement with a normal electric axis, normal P and T waves and a normal QRS in lead V_1. The roentgenogram of the thorax revealed a normal cardiac silhouette, but because of persistent opacity at the base of the right lung, bronchoscopy was performed. All bronchi were patent. The bronchial tree contained some mucoid secretions and it was noted that the bronchi appeared unusually pliable and tended to collapse during expiration. Examination of aspirated secretions for acid-fast bacilli and neoplastic cells gave negative results. The patient was advised to reduce to 180 pounds and to stop smoking.

Case 3: A 28 year old single woman came to the clinic in March, 1955, complaining of dyspnea and cyanosis of recent onset. She had weighed more than 350 pounds for several years. Her parents had noted excessive somnolence at times, and her home physician recently had discovered that she had hypertension and polycythemia.

Her height was 62 inches and her weight was 427 pounds. She was cyanotic, dyspneic at rest, lethargic and somewhat incoherent. Physical examination revealed tachycardia, a blood pressure of 220 mm. of mercury systolic and 150 mm. diastolic, fine rales at the bases of both lungs and normal cardiac tones. There was no pitting edema of the legs. Respirations were rapid, shallow and irregular, with frequent short periods of complete apnea, particularly when she was asleep. Funduscopic examination showed "the neuroretinopathy of acute polycythemia."

Laboratory examinations and tests showed the following results: albuminuria, grade 4; 64 mg. of urea per 100 cc. of blood; carbon dioxide combining power of 29 mEq. per liter; concentration of hemoglobin of 20.5 gm. per 100 cc. of blood; 7,120,000 erythrocytes and 7,800 leukocytes per cubic millimeter of blood; hematocrit reading of 76 per cent; total blood volume of 12,692 cc., and plasma volume of 3,046 cc. A roentgenogram of the thorax showed cardiac enlargement with engorgement of hilar vessels and the electrocardiogram (Fig. 3) showed sinus tachycardia, right axis deviation, high peaked P wave in lead II, a qR ventricular complex in lead V_1, reduced amplitude of QRS complex, and a late R wave in lead aVR.

The arterial oxygen saturation when the patient breathed room air varied periodically from 70 to 90 per cent, but it was constant at 100 per cent when oxygen was breathed (Tables I and II). The central venous pressure was increased (31/15 to 26/15) and the radial arterial blood pressure by direct measurement was 170/74. Arterial dye-dilution curves did not show evidence of shunts, but the circulation time was somewhat prolonged.

Treatment included removal of 2,870 cc. of blood by phlebotomy, use of mercurial diuretics, and anticoagulants, and reduction of weight to 391 pounds. On dismissal she was much improved symptomatically and the concentration of hemoglobin was 16.8 gm. per 100 cc. of blood with a hematocrit reading of 64 per cent.

On return to the clinic in October, 1955, she was asymptomatic and weighed 251 pounds. She was not cyanotic, and physical examination gave negative results except for the blood pressure which measured 190/130. A roentgenogram of the thorax and an electrocardiogram (Fig. 3) did not show any abnormality. She did not have albuminuria; the blood urea was normal and the results of hematologic studies and pulmonary-function studies (Table I) were entirely normal.

She reported in August, 1956, that she had reduced to 135 pounds and felt completely well.

In each of these three cases, a significant degree of arterial hypoxemia was demonstrated. In each instance, this was attributed to the alveolar hypoventilation which was strikingly apparent clinically. Unfortunately, satisfactory quantitative determinations of minute ventilation were not performed. Although the reduced vital capacity characteristic of obesity was noted in the first case, the ventilatory studies were normal in the other two patients. However, the ventilatory studies in Case 3 were performed after a loss of approximately 175 pounds. In each case, loss of weight was accompanied by disappearance of polycythemia and cyanosis, reduction in cardiac size and blood pressure, clearing of adventitious sounds from the thorax, disappearance of albuminuria, return of an elevated blood urea to normal, disappearance of the tendency toward excessive somnolence and reversal of the electrocardiographic evidences of right ventricular overload.

Case 4: A 40 year old man came to the clinic in July, 1951, with the complaints of increasing exertional dyspnea for many years and intermittent edema of the legs during the past year. He had never been orthopneic. He had been obese all his life and had weighed more than 400 pounds for several years.

His height was 70 inches and his weight was 430 pounds. He was plethoric and cyanotic and there was marked pitting edema of the legs. No abnormality of the

TABLE II

STUDIES OF ARTERIAL BLOOD OF THREE OBESE PATIENTS

	Number of Case and Date of Test					
	1 (Dec. 7, 1951)		3 (Mar. 25, 1955)		5 (Jan. 17, 1956)	
	Gas breathed		Gas breathed		Gas breathed	
Factor measured	Air	Oxygen	Air	Oxygen	Air	Oxygen
Oxygen: Content (volume per 100 cc.)	20.4	24.6	17.7	24.8	14.5	20.5
Capacity (volume per 100 cc.)	23.4	23.4	24.6	24.2	21.4	21.4
Saturation (per cent)	87	100	72	100	68	94
Carbon Dioxide: Content (volume per 100 cc.)	56	57	....	....	84	83
Partial pressure in arterial blood (mm. of mercury)	55	70	....	....	61	67
pH	7.36	7.25	....	....	7.46	7.42
Ventilation (liters per minute)	....	....	....	....	13.8	8.3
Tidal volume (milliliters)	....	....	....	....	600	600

heart or lungs was noted on physical examination and the blood pressure was 128 mm. of mercury systolic and 100 mm. diastolic. Funduscopic examination gave negative results. No comment on the ventilatory pattern was recorded.

A roentgenogram of the thorax showed cardiac enlargement and clear lung fields. The electrocardiogram revealed a normal electric axis, a high peaked P wave in lead II and a prominent S in leads I and V_5. Microscopic hematuria and albuminuria, grade 3, were present. The concentration of hemoglobin was 17.8 gm. per 100 cc. of blood on his admission, but this increased to 19.4 gm. after the onset of mercurial diuresis. Erythrocytes numbered 6,010,000 and leukocytes 5,800 per cubic millimeter of blood with a normal differential count and platelet count. The hematocrit reading was 69 per cent. The values for blood urea and serum proteins and the sedimentation rate of erythrocytes were within normal limits. The total blood volume was 12,085 cc., and the plasma volume was 4,109 cc.

On a low-sodium, 800-calorie diet, he lost 22 pounds in 3 days. The use of mercurial diuretics and ammonium chloride caused further loss of weight and resolution of edema. Two weeks after his admission, when his weight had dropped to 364 pounds and he was much improved clinically, studies of pulmonary function were performed (Table I). The vital capacity and expiratory reserve volumes were significantly reduced but there was no spirographic evidence of expiratory obstruction. Arterial oxygen saturations on breathing room air varied from 98 per cent at rest to 95 per cent during exercise, and the arterial saturation increased to 100 per cent on breathing pure oxygen.

Digitalis was administered and 3,000 cc. of blood was removed by phlebotomy. When he was dismissed 6 weeks after admission, he weighed 357 pounds. The concentration of hemoglobin was 14.6 gm. per 100 cc. of blood; erythrocytes numbered 4,790,000 per cubic millimeter of blood and the hematocrit reading was 54 per cent. Roentgenograms of the thorax showed a marked decrease in cardiac size and the blood pressure was 136/86.

By January, 1952, he had reduced to about 300 pounds, and reported that he was feeling very well. He began to regain weight subsequently, and when he returned to the clinic in August, 1953, he weighed 440 pounds and complained of edema of the legs and severe dyspnea on exertion. The blood pressure measured 165/125 and fine rales were heard at the bases of both lungs. Albuminuria and cylindruria were present; the concentration of hemoglobin was 18.1 gm. (after diuresis) and the hematocrit reading was 56 per cent. The value for blood urea was normal. The thoracic roentgenogram showed an increase in cardiac size. He was treated for 3 weeks with mercurial diuretics and a low-sodium, 800-calorie diet. On dismissal, he weighed 385 pounds and was much improved symptomatically. No further follow-up was obtained.

Although hypoxemia was not demonstrated in this case, the studies of pulmonary function were not performed until the patient had had 2 weeks of rest in bed, had been on a reducing diet and had received mercurial diuretics, all of which had resulted in a loss of 66 pounds and decided clinical improvement. The reduced vital capacity and expiratory reserve, and the clinical resemblance of this patient to the patients in Cases 1, 2 and 3 suggest that hypoxemia had been present earlier.

Case 5: A 58 year old man came to the clinic in January, 1956. He had been obese all his life; in 1945 he had weighed 250 pounds and had gained 100 pounds since then. In 1950 he had been treated for mental depression. For years he had had a chronic cough with production of some mucoid and occasionally purulent sputum. He had been troubled with increasing exertional dyspnea for 15 years, had noticed intermittent cyanosis for 7 years, and had had intermittent edema of the legs for 5 years. He had been treated for pneumonia by his home physician in November, 1955, at which time polycythemia was diagnosed. Results of studies of pulmonary function had been reported to be normal. His family had noted excessive lethargy and somnolence in the past few years.

His height was 68 inches and he weighed 335 pounds. He was awake and rational but was dyspneic at rest and had a wheezy cough. Cyanosis was marked. The thorax expanded poorly with maximal inspiratory effort and expiratory rales were heard over both lungs. Cardiac sounds were distant and there was marked pitting edema of the feet and legs. Blood pressure was 226 mm. of mercury systolic and 130 mm. diastolic; respirations were 28 per minute and shallow, and the pulse rate was 120 per minute. Funduscopic examination showed cyanosis of the retinas due to polycythemia or to right-sided cardiac failure, plus minimal hypertensive changes.

Albuminuria, grade 2, was present and the value for blood urea was 24 mg. per 100 cc. The concentration of hemoglobin was 15.6 gm. per 100 cc. of blood and the erythrocytes numbered 6,150,000 and the leukocytes 7,200 per cubic millimeter of blood. The hematocrit reading was 63 per cent and the sedimentation rate of erythrocytes was 7 mm. in the first hour (Westergren method). Total proteins measured 6.6 gm. per 100 cc. of serum. The value per liter of serum for sodium was 133 mEq.; for potassium, 4.9 mEq.; for carbon dioxide combining power, 25 mEq., and for chlorides, 88.5 mEq. The pH of venous blood was 7.36. A roentgenogram of the thorax showed pulmonary congestion and slight cardiac enlargement, and an electrocardiogram showed normal axis deviation with tall peaked P waves in leads II and III.

The day after his admission to the hospital, fever developed (102° F.) and his condition deteriorated seriously. Respirations became wheezy and irregular and he began to cough up varying amounts of thick tenacious purulent sputum. He became semicomatose, disoriented and confused, and the cyanosis increased. Crepitant raies could be heard over both lung fields.

He was treated with digitalis, antibiotics, mercurial diuretics, aminophyllin given intravenously, oxygen by nasal catheter at a rate of 1 to 4 liters per minute and intermittent positive pressure breathing with oxygen and isuprel aerosol for 10

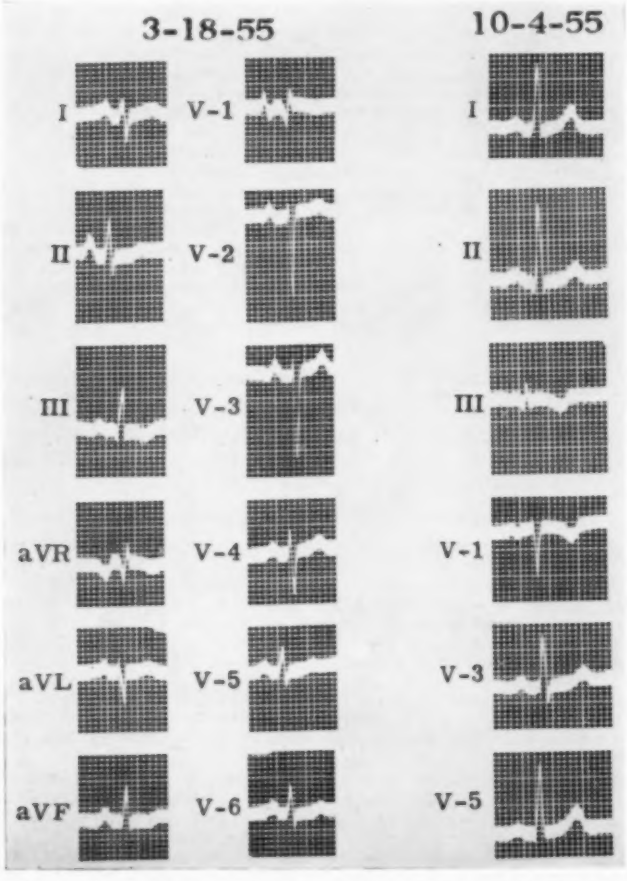

FIGURE 3: Electrocardiograms for a 28 year old woman (Case 3) before and after a loss of 176 pounds.

minutes every hour. Sputum was raised with the aid of a Barach cofflator and, on one occasion, by direct aspiration of the tracheobronchial tree by means of a laryngoscope. Caloric intake was minimal and a total of 1,500 cc. of blood was removed in four phlebotomies, after which the concentration of hemoglobin was still 15.4 gm. and the hematocrit reading, 61 per cent. The patient was semicomatose for 3 weeks, during which his respirations were irregular and sometimes Cheyne-Stokes in type. The administration of oxygen greatly decreased the cyanosis. Whenever the use of oxygen was discontinued, his respirations would become deeper for a period, but after about an hour he seemed to tire and the cyanosis would become more marked. The carbon dioxide combining power measured as high as 39.5 mEq. per liter, and the value for urea was 72 mg. per 100 cc. of blood on one occasion.

One week after his admission, respiratory minute volumes and arterial blood samples were studied (Table II). On breathing room air, the total ventilation was 13.8 liters per minute, there was marked arterial hypoxemia and hypercapnia and the pH was 7.46. On breathing pure oxygen, the respiratory minute volume decreased to 8.3 liters, the arterial oxygen saturation rose to 94 per cent, $P_{a}co_{2}$ increased and the pH fell to 7.42.

By the fourth week of hospitalization, the patient had shown considerable improvement clinically, manifested by loss of edema, loss of 45 pounds, marked reduction in dyspnea and cyanosis, almost complete clearance of auscultatory abnormalities from the thorax, subsidence of fever and diminished disorientation and somnolence. The blood pressure was frequently within the normal range. He was out of bed for short periods and the use of oxygen was discontinued. The concentration of hemoglobin was 13.5 gm. with a hematocrit reading of 48 per cent; the value for urea decreased to 30 mg. per 100 cc. of blood and the carbon dioxide combining power decreased to 29 mEq. per liter. At this time, the total blood volume was 8,428 cc. and the plasma volume was 3,877 cc.

Four weeks after admission, severe thoracic pain, dyspnea and shock developed while the patient was walking about his room. An electrocardiogram showed the pattern of partial right bundle branch block and nodal tachycardia with atrioventricular dissociation. Death occurred 2 hours later.

At necropsy, a large embolus was found which filled the pulmonary trunk and extended into both pulmonary arteries. There were small recently formed emboli in the lower lobe of the right lung with areas of fresh infarction. The heart weighed 570 gm. and both ventricles showed some hypertrophy. Coronary sclerosis was slight to moderate. Some purulent bronchitis throughout both lungs and minimal bronchiectasis in the right lower lobe were observed, but the pulmonary parenchyma was normal except for congestive changes and some scattered areas of emphysema. The large muscular branches of the pulmonary arteries showed medial hypertrophy (Fig. 4). Sections of the intercostal muscles did not reveal abnormalities.

Although this patient undoubtedly had chronic bronchitis with bronchiectatic changes, it seems likely that obesity was an important factor in the genesis of his ventilatory dysfunction. When he first presented at the clinic, he appeared to be hypoventilating. The exacerbation of his chronic endobronchial infection, manifested by fever, production of purulent sputum and marked clinical deterioration, critically compromised his already impaired ventilatory function, probably by plugging certain bronchi to produce regional alterations of the ventilation-perfusion ratio and "functional shunts" in the lungs. The presence of functional shunts would explain the following: (1) his inability to overcome the hypoxemia and hypercapnia on breathing room air with a ventilatory minute volume of 13.8 liters (tidal volume, 600 ml.), and (2) the failure of his arterial oxygen saturation to rise above 94 per cent when he breathed pure oxygen at 8.3 liters per minute. Necropsy did not show evidence of alveolar-capillary block, and the pulmonary emboli appeared to be merely a terminal phenomenon on clinical, electrocardiographic and pathologic grounds. It is suggested that the mechanical effects of his obesity on respiration prevented him from making a more adequate ventilatory response to the arterial hypoxemia and hypercapnia. The arterial pH values were interpreted as follows: Prior to the arterial blood studies,

the patient had breathed an oxygen mixture for 6 days and presumably had compensated his respiratory acidosis by the usual renal mechanisms. On breathing room air, the consequent relative hyperventilation lowered the P_{aCO_2} sufficiently that the respiratory acidosis was temporarily overcompensated, and the arterial pH was actually in the alkaline range (7.46). When he then breathed pure oxygen, the total ventilation was divided almost in half, and the arterial pH decreased toward the normal range again.

Case 6: A 48 year old man first came to the clinic in July, 1955, complaining of increasingly severe exertional dyspnea since 1950. He was a heavy smoker and had had a chronic cough for 15 years. He had weighed more than 200 pounds for 15 years or more. He had been hospitalized in 1951 because of congestive heart failure, at which time he weighed 250 pounds, was cyanotic and drowsy, and apparently had become very disoriented and confused while in an oxygen tent. Roentgenograms of the thorax did not show evidence of abnormality. He was given mercurial diuretics and lost 30 pounds. In 1954, he was again hospitalized and treated for congestive cardiac failure.

His height was 68 inches and he weighed 240 pounds. He was plethoric, drowsy and moderately cyanotic, and his respirations were rapid, shallow and grunting. The pulse rate was 100 beats per minute and the blood pressure was 130 mm. of mercury systolic and 80 mm. diastolic. Cardiac murmurs were not heard, but the second sound at the pulmonic area was louder than at the aortic area. Inspiratory rales and expiratory rhonchi were heard over both lungs. He had some ascites and moderate pitting edema of the legs. The thorax expanded poorly on inspiration. Funduscopic examination showed "cyanosis retinae."

Urinalysis gave normal results, but the value for blood urea was 72 mg. per 100 cc. The concentration of hemoglobin was 15.4 gm. per 100 cc. and leukocytes numbered 4,100 with a normal differential count. The carbon dioxide combining power was 24 mEq. per liter. A roentgenogram of the thorax showed pulmonary vascular congestion and cardiac enlargement. An electrocardiogram showed right axis deviation, tall peaked P waves in leads II and III, prominent S deflections in leads I, V_5 and V_6, and inversion of T waves with depression of ST segments from leads V_1 and V_4. The pattern seen was consistent with that of right ventricular overload.

The patient was put in an oxygen tent and it was noted that he became more lethargic and confused. He gradually improved on digitalis, mercurial diuretics, aminophyllin and a reducing diet. Ten days after his admission, the concentration

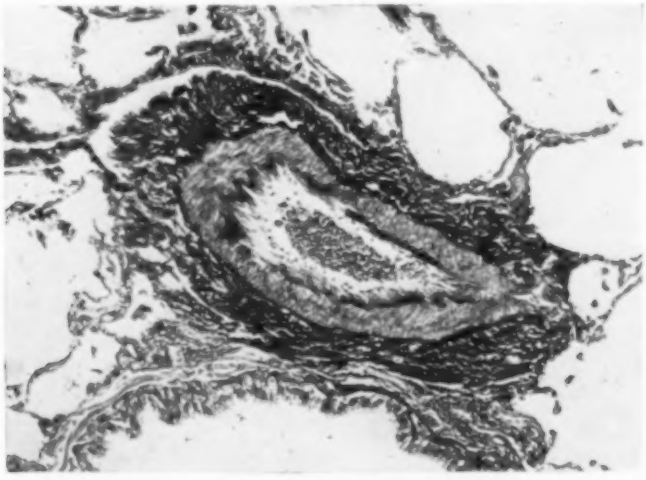

FIGURE 4: View of tissue from the right lung of a 58 year old man (Case 5), showing medial hypertrophy in a large muscular artery (stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain; X100).

of hemoglobin was 17.9 gm. and the value for urea was 48 mg. per 100 cc. of blood; the carbon dioxide combining power was 30 mEq. per liter. Three phlebotomies totaling 1,500 cc. of blood were performed, after which the hematocrit reading was 64 per cent.

Studies of pulmonary function (Table I) 2 weeks after admission showed reduced vital, total and maximal breathing capacities but the residual volume was increased and the nitrogen washout index was abnormal. Arterial oxygen saturation was 84 per cent at rest and decreased to 80 per cent on exercise while breathing room air, but increased to 100 per cent on breathing oxygen. There was moderate expiratory slowing but no air trapping. The minute ventilation on oxygen was 12 liters, with a tidal volume of 660 ml.

On dismissal a week later, he weighed 191 pounds and felt greatly improved.

Studies of pulmonary function of this patient suggest that he had intrinsic pulmonary disease, but the abnormalities demonstrated are not definitively diagnostic. The striking reduction in maximal breathing capacity is somewhat out of proportion to the degree of airway obstruction demonstrated, and suggests a mechanical restriction of ventilation. The achievement of 100 per cent saturation on breathing pure oxygen rules out significant cardiovascular shunts. It was considered that this patient's obesity played a significant, if not the major role, in his respiratory dysfunction.

Case 7: A 46 year old dairyman came to the clinic in August, 1953, because of exertional dyspnea and easy fatigability. For many years he had had chronic asthmatic bronchitis with production of thick sputum on coughing. In the 10 years prior to registration at the clinic his weight had risen from 190 to 276 pounds, but he had recently lost 30 pounds by dieting.

His height was 69 inches and his weight was 246 pounds. The blood pressure was 140 mm. of mercury systolic and 104 mm. diastolic; he was plethoric; many rhonchi, dry rales and wheezes were heard over the chest and cardiac sounds were distant. The retinal veins appeared congested on funduscopic examination.

The concentration of hemoglobin was 16.6 gm. per 100 cc., with an erythrocyte count of 4,830,000, a leukocyte count of 8,500 and a hematocrit reading of 64 per cent. The total blood volume was 9,517 cc. and the plasma volume was 3,426 cc. A roentgenogram of the thorax showed cardiac enlargement with some passive congestion of the lungs, and an electrocardiogram showed slight left axis deviation with a prominent P wave in lead II.

Vital capacity, total lung capacity, expiratory reserve volume and maximal breathing capacity were reduced and the residual volume and the nitrogen washout index were elevated (Table I). Spirographic evidence of severe expiratory obstruction was observed. Arterial desaturation occurred when the patient was at rest and increased during exercise, but the saturation rose to 100 per cent when pure oxygen was breathed. The minute ventilation on oxygen was 6 liters, with a tidal volume of 390 cc.

The patient was advised to reduce weight, and measures to control his asthmatic bronchitis were prescribed.

He was examined again in August, 1954, at which time he complained that the dyspnea had increased in severity. He weighed 260 pounds, the concentration of hemoglobin was 19.1 gm. and the hematocrit reading was 74 per cent. The leukocyte and platelet counts were normal, but the total blood volume was 11,373 cc. A total of 2,500 cc. of blood was removed in five phlebotomies, which lowered the hematocrit reading to 63 per cent and caused some symptomatic improvement. He was given 4 mc. of radiophosphorus, and urged to reduce weight and stop smoking.

He reduced his weight to 215 pounds by January, 1955, and stayed at that weight for the subsequent year. Repeated hematologic examinations by his home physician showed normal results. He felt well, had minimal dyspnea and was able to carry on his usual occupation. In the spring of 1956 he gained 10 pounds in weight and noted increased dyspnea, cough and expectoration. The concentration of hemoglobin increased to 16.8 gm.

In June, 1956, he weighed 230 pounds and inspiratory and expiratory rhonchi were heard over the chest. The roentgenogram of the thorax was without abnormality, but the hematocrit reading was 63 per cent. Plasma clearance of radioiron was indicative of absolute polycythemia. Two phlebotomies were performed, radiophosphorus was administered, and he was again urged to lose weight.

The results of studies of pulmonary function, while not diagnostic, are consistent with the findings in asthmatic bronchitis plus early emphysema

and fibrosis. The clinical improvement associated with the loss of weight and the recurrence of symptoms with gain suggest that obesity may have been a considerable factor in aggravating the effects of this patient's chronic pulmonary disease.

Case 8: A 66 year old attorney came to the clinic in July, 1956, for further orthopedic treatment of a fracture-dislocation of the left humerus incurred in 1948. He had been obese for many years, and had weighed more than 300 pounds on several occasions. He had had exertional dyspnea for years. In 1954, he was treated for "chest congestion" with antibiotics. A roentgenogram of the thorax did not show evidence of any abnormality, but an electrocardiogram showed inverted T waves from leads V_4 to V_6. In May, 1956, he again had an episode of "chest congestion" and was given digitalis, with some improvement in his dyspnea.

His height was 67 inches and he weighed 300 pounds. He had dyspnea on mild exertion but no plethora or cyanosis. The lungs and heart appeared normal on physical examination and the blood pressure was 150 mm. of mercury systolic and 70 mm. diastolic. There were muscular atrophy and stiffness of the joints in the left hand and shoulder.

The hemoglobin measured 13.6 gm. per 100 cc. of blood and the erythrocyte sedimentation rate was 66 mm. in the first hour (Westergren method). The values for blood urea and serum proteins were normal. Albuminuria, grade 2, was present. A roentgenogram of the thorax appeared normal. The electrocardiographic findings of left axis deviation and inverted T waves in leads II, III, V_4, V_5 and V_6 were interpreted as indicating left ventricular hypertrophy.

The patient was placed on a reduction diet of 800 calories and the use of digitalis was continued. A loss of 25 pounds occurred in a month, at which time tests for pulmonary function were performed (Table I). The vital capacity, expiratory reserve volume and maximal breathing capacity were greatly reduced, and the residual volume was slightly increased. Air trapping was not present and expiratory slowing was minimal. The arterial oxygen saturation was 97 per cent at rest, decreased to 93 per cent after 3.5 minutes of exercise on breathing room air and increased to 100 per cent on breathing pure oxygen. The minute ventilation on air was 13 to 14 liters at rest and this increased to 40 liters per minute after 3 minutes of exercise.

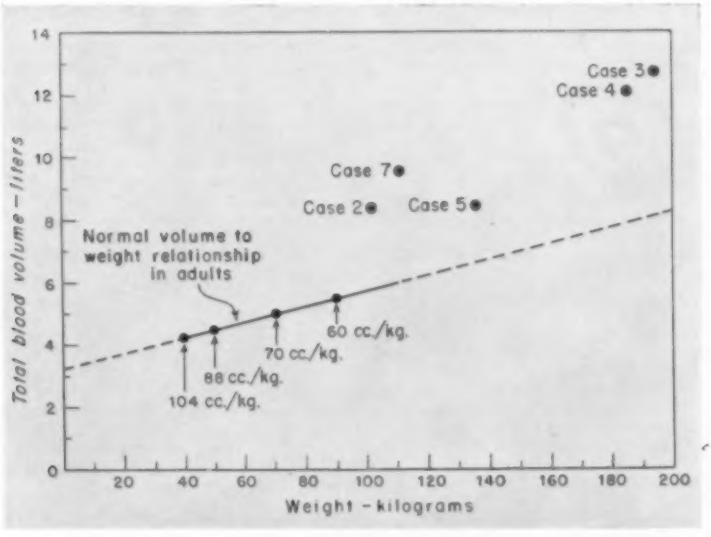

FIGURE 5: Graphic relationship of total blood volumes in five obese persons to normal blood volume-weight regression line (derived from the data of Funkhouser and associates.[21]) Extrapolated portions of regression line are indicated by dots. The numeral beside each plotted total blood volume indicates the case number. In Case 5, the plotted value does not include 1,500 ml. of blood removed previously by phlebotomies.

The lung volumes in this case are compatible with those found in cases of extreme obesity. The marked reduction in maximal breathing capacity in the absence of obstruction in the airway and the inability of the patient to ventilate sufficiently during exercise to maintain a normal arterial saturation is strong evidence in favor of a mechanical restriction of ventilatory capacity. The normal nitrogen washout index and the absence of significant expiratory slowing rule out chronic obstructive emphysema. Although the history suggests that pulmonary congestion of cardiac origin might have been present in this patient, it has been shown[23] that exertional dyspnea of cardiac origin is not accompanied by significant reductions in vital capacity or maximal breathing capacity in the absence of signs of congestive failure.

Comment

The mechanism by which obesity produces respiratory insufficiency is of great theoretical interest. The immediate cause of the arterial hypoxemia appears to be alveolar hypoventilation, which has been a prominent feature of those reported cases with complete studies of pulmonary function.[10, 12, 13] In the Cases 1, 2 and 3 of this report, hypoventilation was diagnosed on clinical grounds, but adequate studies of minute ventilation were not performed. Sieker and associates[12] suggested that the reduced functional residual capacity which has been recorded in some cases may be a contributory factor in that the lung volume "may be inadequate to prevent marked swings in arterial oxygenation with shallow breathing."

A reduced vital capacity, which has been attributed to diaphragmatic elevation and mediastinal deposition of fat,[3, 9] has been an almost constant finding in the reported cases of obesity with polycythemia, but it is not clear how a reduction in vital capacity, per se, can cause alveolar hypoventilation and hypoxemia. It is well known that patients with certain neuromuscular diseases may exhibit large decreases in vital capacity and yet maintain a normal arterial oxygen saturation at rest. In a large series of patients studied at the Mayo Clinic at varying intervals after pneumonectomy, arterial oxygen saturations were invariably normal when the patient was at rest despite striking reductions in vital capacities and functional residual capacities.[24] Even during the standard exercise test, a significant decrease in arterial oxygen saturation was infrequent in these patients.

Kerr and Lagen[4] postulated that obesity causes lumbar lordosis and thoracic kyphosis which lead to postural emphysema. It has never been shown that the ill-defined condition known as postural emphysema can lead, in itself, to arterial hypoxemia. Mack and Snider[25] stated that thoracic kyphoscoliosis never leads to chronic cor pulmonale in the absence of recurrent bronchial infections with the development of chronic obstructive emphysema. Spirographic evidence of obstruction of the airway

has not been a conspicuous feature in the reported cases of obesity with polycythemia.

Other authors[10, 13, 14] have suggested that alveolar hypoventilation in extreme obesity is a result of impaired ventilatory mechanics. Although there are no reported studies on the work of breathing in obese persons, it is reasonable to assume that deposits of fat on the thoracic wall and in the abdomen could significantly increase the mechanical work of breathing, and hence the consumption of oxygen. The almost universal presence of dyspnea in the obese would support this concept.

It can be postulated that the mechanical effects of extreme obesity upon ventilation may, in some instances, be accompanied by such an increase in the work of breathing that the respiratory centers maintain alveolar ventilation at a suboptimal level in order to decrease the work load. This suboptimal level permits alveolar and other bodily carbon dioxide tensions to increase, and may represent a compromise between the abnormally large amount of work required to accomplish ventilation and the tendency of the respiratory center to prevent accumulation of carbon dioxide by increasing alveolar ventilation. That a normal respiratory center will permit elevated arterial levels of carbon dioxide to persist when the work of breathing is abnormally increased has been demonstrated by Cherniack and Snidal,[26] who found that artificial increases of airway resistance in normal persons greatly reduced the ventilatory response to inhaled carbon dioxide.

In extreme obesity, the mechanical restriction of ventilation might be manifested by failure of ventilation to increase adequately during exercise (as in Case 8) and later by alveolar hypoventilation at rest. The consequent hypercapnia would eventually diminish further the sensitivity of the respiratory centers and thus tend to perpetuate the hypoventilation. The functional nature of the entire process is shown by (1) the ability of one patient (Case 1) to achieve normal arterial oxygen saturation on voluntary hyperventilation and (2) the repeated reports of complete recovery after adequate loss of weight (as in Case 3).

In Cases 5, 6 and 7 the minute ventilation, though of sufficient magnitude to maintain oxygenation in normal persons, was not adequate to prevent arterial oxygen desaturation in these three patients who had diseased lungs. It is postulated that the increased work of breathing due to obesity prevented these patients from achieving a more adequate ventilatory response to hypoxemia and hypercapnia caused by intrinsic pulmonary disease.

The cardiovascular manifestations of the syndrome are of interest. Clinical signs of congestive failure have been noted in several reported cases. Cardiac catheterization in three cases[10, 12] revealed pulmonary hypertension which was attributed to chronic arterial hypoxemia. Electrocardiographic evidence of right ventricular hypertrophy or strain has been noted commonly, and right ventricular dilatation and hypertrophy was demonstrated at necropsy in one instance.[27] For these reasons, the

signs of congestive failure have been attributed to right heart failure. Although cardiac catheterization was not performed on any patients in the present series, the repeated electrocardiographic findings of right ventricular overload which improved with loss of weight and the pathologic demonstration of hypertrophy of the pulmonary arterioles in Case 4 are confirmatory evidence that pulmonary hypertension is commonly present. However, the possible presence and importance of left cardiac failure cannot be summarily dismissed. In Cases 2, 3 and 4, the findings on physical examination were suggestive of pulmonary congestion, and dye curves in Cases 1 and 3 showed prolonged circulation time. The deleterious effect of obesity on cardiac disease is well documented,[3, 28, 29] and in a pathologic study of the hearts of 139 obese patients, Smith and Willius[30] reported four cases in which frank congestive failure had occurred in the absence of organic heart disease, necropsy demonstrating only fatty deposits in the subepicardium with some fatty infiltration between the muscle bundles. Pulmonary congestion and edema may lower the vital capacity and maximal breathing capacity[31] and increase the work of breathing.[32] Thus pulmonary congestion, whether due to left ventricular failure or to polycythemia, would tend to decrease alveolar ventilation even further. In several cases of the present series, phlebotomy and control of cardiac failure with the use of digitalis and mercurials appeared to bring about considerable clinical improvement before any great reduction in weight had been achieved.

Arterial hypertension which diminished with loss of weight was found in Cases 1, 3 and 5. Although a high incidence of hypertension has been reported among obese persons,[3, 28, 29] it has been shown[33-35] that indirect recordings of arterial pressure with the standard 13 cm. cuff often give erroneously high values in these persons. In Case 3, the blood pressure measured directly with an intra-arterial needle was strikingly lower than the indirect measurements.

Polycythemia noted in patients in the present series and in series previously reported appears to be secondary rather than primary. This concept is supported by (1) the absence of leukocytosis, thrombocytosis, myeloid immaturity and splenomegaly, (2) the presence of arterial hypoxemia and (3) the tendency of the polycythemia to correct itself after weight is reduced and arterial oxygen saturations return to the normal range. The values for total blood volume in the present series, when calculated on the basis of actual weight, are within the accepted range. However, it has been shown recently[27] that the regression line relating total blood volume to body weight, while linear, does not pass through the intersection of the co-ordinates. Therefore, the volume of blood per kilogram of body weight is not constant at different weight values; the blood volume per kilogram body weight for thin people is higher than the "normal" value and that of obese people is lower. The graphic plots of total blood volume against weight were significantly above the true regression line in each of the five cases in this series in which blood volume was studied, indicating absolute polycythemia (Fig. 5).

SUMMARY

Marked obesity may be associated with alveolar hypoventilation, arterial hypoxemia, hypercapnia and secondary polycythemia in the absence of primary pulmonary or cardiac disease. Pulmonary hypertension and right cardiac failure may develop secondarily. Appropriate loss of weight is accompanied by reversal of these complications. In patients with primary pulmonary or cardiac disease, obesity aggravates the dysfunction and loss of weight may produce considerable clinical improvement.

The cases of eight obese patients studied at the Mayo Clinic are reported. In four patients, obesity and secondary polycythemia were present without intrinsic pulmonary disease. In three patients with primary pulmonary disease, obesity was thought to have played a significant role in the development of hypoxemia and secondary polycythemia. One patient did not have polycythemia but tests of pulmonary function suggested that he manifested the early stages of ventilatory impairment of obesity.

It is suggested that the mechanical effect of obesity in increasing the work of breathing is the primary factor in the genesis of the alveolar hypoventilation which appears to be the significant abnormality.

RESUMEN

La obesidad marcada puede asociarse con hipoventilación alveolar, hipoxemia, hipercapnia y policitemia secundaria en auscenia en ausencia enfermedad primaria respiratoria o cardiaca. La hipertensión pulmonar y la insuficiencia cardiaca derecha pueden desarrollarse mástarde. La pérdida de peso adecuadamente obtenida se acompaña de mejoría de estas complicaciones. En los enfermos con enfermedad primaria pulmonar o cardiaca la obesidad agrava la disfunción y la pérdida de peso produce mejoría considerable.

Se relatan los casos de ocho enfermos obesos estudiados en la Clínica Mayo. En cuatro enfermos la obesidad y la policitemia secundaria se encontraron sin enfermedad pulmonar intrínseca. En tres enfermos con enfermedad pulmonar primaria se pensó que la obesidad desempeñó un papel de significación en el desarrollo de hipoxemia y policitemia secundaria.

Un enfermo no tuvo policitemia pero las pruebas de función pulmonar sugirieron que manifestaba los inicios de una insuficiencia ventilatoria de la obesidad.

Se sugiere que el efecto mecánico de la obesidad al aumentar el trabajo de la respiración es el factor primario en la génesis de la hipoventilación alveolar que parece ser la anormalidad significante.

RESUME

Une obésité accentuée peut être associée à une hypoventilation alvéolaire, à l'hypoxémie artérielle, à l'hypercapnée et à la polycythémie en l'absence d'affection initiale pulmonaire ou cardiaque. Une hypertension pulmonaire et une atteinte cardiaque droite peuvent survenir secondairement. Une perte de poids proportionnée suit la régression de ces compli-

cations. Chez les malades atteints d'affection initiale pulmonaire ou cardiaque, l'obésité aggrave le dysfonctionnement et la perte de poids peut amener une amélioration clinique considérable.

Les auteurs rapportent les cas de huit malades obèses étudiés à la Clinique Mayo. Chez quatre malades, l'obésité et la polycythémie existaient sans affection pulmonaire initiale Chez trois malades atteints d'affection pulmonaire primitive l'obésité fut considérée avoir joué un rôle indiscutable dans l'apparition de l'hypoxémie et de la polycythémie secondaire. Un seul malade n'était pas atteint de polycythémie mais les tests de la fonction pulmonaire montrèrent qu'il présentait les premiers symptômes d'un trouble ventilatoire dû à l'obésité.

Les auteurs pensent que l'effet mécanique de l'obésité, en augmentant le travail respiratoire, est le premier facteur dans le génèse de l'hypoventilation alvéolaire qui parait à première vue être l'anomalie essentielle.

ZUSAMMENFASSUNG

Ausgeprägte Fettsucht kann verbunden sein mit alvaeolärer Hypoventilation, arterieller Hypoxaemie, übermässi hohem Kohlensäuregehalt des Blutes und sekundärer Polycytaemie beim Fehlen primärer pulmonaler oder cardialer Erkrankung. Pulmonale Hypertension und Versagen des rechten Herzens können sich sekundär entwickeln. Ein angemessener Gewichtsverlust ist verknüpft mit einer Behebung dieser Komplikationen. Bei Kranken mit primärer pulmonaler oder cardialer Erkrankung verschlimmert die Fettsucht die Funktionsstörung, und ein Gewichtsverlust kann eine beträchtliche klinische Besserung bewirken.

Es wird berichtet über Fälle von 8 fettsüchtigen Kranken, die in der Mayo-Klinik untersucht wurden. Bei 4 Kranken lagen Fettsucht und sekundäre Polycytaemie vor ohne wesentliche Lungenerkrankung. Bei 3 Patienten mit primärer Lungenerkrankung wurde bezüglich der Fettsucht angenommen, dass diese eine beträchtliche Rolle gespielt habe bei der Entwicklung der Hypoxaemie und sekundären Polycytaemie. Ein Patient hatte zwar keine Polycytaemie, aber die Lungenfunktionsprüfungen machen es wahrscheinlich, dass bei ihm die frühen Stadien ventilatorischer Schädigung durch Fettsucht manifest waren.

Es wird die Vermutung ausgesprochen, dass die mechanische Wirkung der Fettsucht mit ihrem Anstieg der Atemtätigkeit der primäre Faktor bei der Genese der alveolären Hypoventilation ist, die die bezeichnende Abweichung von der Norm zu sein scheint.

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Use and Abuse of Skin Tests in Allergic Conditions of the Respiratory Tract*

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Introduction

In recent years I have had the privilege of addressing chapters of the American College of Chest Physicians in Europe, Asia, South America, and my own United States. Almost all the members of these chapters are well versed in all branches of their specialty, with one exception, i.e. allergy.

For some reason the average chest physician (and also the average general internist) pays little attention to allergic factors. This indifference seems to apply even when the patient has a definite allergic condition, e.g. bronchial asthma, seasonal or perennial allergic rhinitis, nasal polyposis, allergic bronchitis and tracheitis, and including many cases of asthmatic bronchitis.

Most of these physicians seem content to make a diagnosis of bronchial asthma, for example, by the history, examination and clinical and laboratory tests. They try to find the cause of symptoms by the history and clinical trials, as by removal of the dog or cat. If that is successful they seem pleased, but most are content and go no further. If this halfway method does not reveal the cause of the asthma, those physicians who are not allergy-minded are apt to treat symptomatically by various medications, including antihistaminic and antibiotic drugs and oxygen.

The recent introduction of the steroid drugs (ACTH, cortisone, and prednisone) has given us an additional valuable tool in this field. Many physicians, however, including some allergists, are using these steroids much too often. Albert Rowe[1] of California recently wrote me as follows: "I am very much afraid that the use of steroids is going to have a retarding influence. The challenge of physicians at the present time still remains in the actual determination of specific causes of these allergic manifestations rather than in their easy relief with steroid therapy."

Rowe is absolutely correct. Over these many years we have usually found the cause of the allergic symptoms by allergy survey, and have been able to relieve the symptoms in most patients by removing the cause as far as possible, with or without supplementary hyposensitization. In all fields of medicine we try to find the cause and to remove it—why should we not use every effort and follow every clue in the field of allergy as in other branches of medicine?

*Presented at the Fourth International Congress on Diseases of the Chest, American College of Chest Physicians, Cologne, Germany, August 19-23, 1956.

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Fortunately, we have excellent methods for investigating bronchial asthma and other allergic conditions. Our first question is, "What is the diagnosis?" Our second question is, "What is the cause?"

We urge all physicians to look for allergy in every patient who has chronic or acute dyspnea, or who has chronic or acute rhinitis, sinusitis, bronchitis, or laryngitis. That patient is entitled to a thorough allergy survey. This includes a search for:

(a) History of some allergic condition in the patient or his family.
(b) Eosinophilia in the blood, sputum and/or nasal smear.
(c) Seasonal aspects or incidence.
(d) Clinical tests, e.g. removal of a dog or of egg-containing foods.
(e) Skin tests.

We recommend that all internists, including those especially interested in chest diseases, carry out skin tests in all patients who are allergic or suspected of being so. If the physician cannot carry out these tests himself, he is duty bound to refer the patient to another physician who is equipped with skin test material. That doctor should make the allergy survey, and, if desired, return the patient to the referring physician, along with a letter outlining precautions against house dust, pollens, foods, fungi, animal danders, etc. The allergist should also send any necessary extracts, with dosage schedules, if hyposensitization (desensitization) is deemed advisable; and, if possible, he should see the patient from time to time to give stronger extracts and to make sure that the patient is actually following orders.

Chest physicians will be well advised to give more attention to allergy, e.g. to learn more about local pollens and fungi, and to note both allergic and psychic conditions when they visit a patient's home. They should attend lectures and courses in the field of allergy and read more papers on this important subject. Approximately 10 per cent of the population is allergic in one way or another.

Now let me mention briefly something about the good and the bad points of skin tests themselves.

Techniques

Skin tests are usually carried out either by scratch or intracutaneous methods, or by both. Information can also be obtained by using the passive transfer technique, by conjunctival and nasal tests, and by clinical experiments.

Skin tests offer us a valuable short cut, and often reveal causes which cannot be found even after a searching history and clinical trials. All positive skin tests, however, must be corroborated clinically.

A. *Scratch (Cutaneous) tests* were first carried out by Blackley of England in 1873,[2] with positive reactions to grass pollen in those who had hay fever and/or asthma during grass-pollinating seasons. Previously, however, Hyde Salter[3] had noted positive reactions in his own skin from the scratch of a cat's paw. In this century rapid progress has been made in skin testing. In 1912 Schloss,[4] found positive reactions

in a child who was allergic to egg, almond, and oat. Walker[5] in 1916 reported 400 patients with asthma, and divided them into two groups: sensitive, with positive skin tests, and nonsensitive, in whom the scratch tests were negative.

Scratch tests have proved extremely valuable all through these many years. They are not perfect, but they are widely used, are safe, and can be done easily. The materials are either liquids which are rubbed into a scratch, or powders which are dissolved with N/10 sodium hydroxide and then rubbed into the scratch.

B. *The Intracutaneous (Intradermal) Method* was started and popularized by Cooke and his associates[6] in 1915. Their students have continued to use this intradermal method; those who followed Schloss and Walker have used the scratch technique. For many years controversy has existed between the exponents of these two procedures, and even to this day many allergists use only one or the other. Fortunately, most of us have learned the good points of each method, and we use both techniques.

Intracutaneous tests are done with sterilized solutions, needles and syringes. Larger reactions are usually obtained by these injections into the skin, and frequently we find a positive intradermal test after a scratch test for the same allergen has been negative.

Systemic reactions and even death have occasionally occurred when intradermal tests have been made without a previous negative scratch test. Swineford,[7] for example, reported death in one patient and anaphylactic shock in another—both received intradermal tests with a mustard extract and neither patient had previously been tested for mustard by the scratch method. Swineford concluded his article by stating, "Every intradermal test should be preceded by the less sensitive scratch test."

We believe that scratch tests should be made first. If that technique gives us enough information, intradermal testing is not necessary. For example, if hay fever and asthma occur each year when the grasses are pollinating, and if scratch tests are strongly positive for the various grass pollen extracts, intradermal testing with these extracts is not necessary and, in fact, could cause systemic reactions. If, however, scratch testing does not yield sufficient information, testing by the intracutaneous method must follow, and will frequently be successful even though the scratch test was negative. To solve some allergic problems, one frequently has to use every available method, just as one does who tries to solve a murder mystery. The allergist is a detective.

C. The *Passive Transfer* method was invented in 1921 and named after its authors, Prausnitz and Küstner.[8] "The substance responsible for the immediate positive skin reaction in hay fever and asthma is present in the patient's blood and can be transferred to and fixed in a normal skin by an intracutaneous injection of the patient's serum. This antibody, designated as *atopic reagin* by Coca and Grove,[9] is specific for each atopen" (Walzer[10]).

This indirect method of testing by no means takes the place of the

usual scratch and intracutaneous techniques. It need be used only occasionally, when direct testing is impractical, especially when the patient's skin is covered with eczema or cannot be used because of severe dermographia.

D. The *Conjunctival* method is occasionally used to test pollens, fungi, or animal danders, but is only tried when both the scratch and intracutaneous techniques have proved negative.

E. The *Nasal* method can be tried with such materials as fungi or perfumes.

Value of Skin Tests in Allergy of the Respiratory Tract

Skin tests are indispensable in these allergic conditions. Positive reactions are usually obtained when the history indicates allergy to a specific food or inhalant material, and when the test is positive the patient's suspicions are verified to the satisfaction of the patient and the physician. Some physicians seem content with the patient's observation that egg, for example, causes his asthma. Occasionally, in such a case, the skin test to egg extract proves negative both with the scratch and intradermal techniques—and then one looks for a different cause—the asthma may be due not to the egg but to bacon which has been in the same pan.

No physician has time or inclination to ask regarding every possible cause for symptoms. In one of our patients, for example, we were able to relieve asthma by removing a dental adhesive used to keep his upper plate in position. This adhesive contained karaya gum. The patient gave a four-plus reaction to karaya gum extract which we had not previously suspected. Cottonseed protein is a rather frequent cause of severe asthma, yet the cottonseed-sensitive patient does not suspect this unless he has had previous skin tests. Removal of cottonseed and impure cottonseed oils usually brings almost immediate relief. Some patients complain of hay fever, but their seasons may not be exactly synchronous with those of the usual pollens; in such cases skin tests frequently indicate that molds and smuts cause or aggravate symptoms, and the patient needs hyposensitization with extracts of these fungi, instead of pollen.

Skin tests are not infallible. Occasionally they are negative even though clinically one can prove that the patient is allergic. In other cases, especially with food extracts, positive skin tests may occur, yet are unrelated to the cause of symptoms.

The positive skin test constitutes just another clue, but a valuable one. It usually indicates a clinical allergy, but this allergy may be past, present or future. The student of allergy soon learns this fact, and he also learns that positive skin tests in dermographic skin must be minimized.

He also learns that skin tests are frequently lessened in size or absent in asthmatic patients who are receiving such medication as ephedrine, epinephrine, or antihistaminic drugs. He therefore postpones skin testing in such cases until these drugs are presumably out of the system (three to seven days).

Nevertheless, and despite these relatively slight limitations, skin tests, when well done and thoroughly carried out, are indispensable in the field of allergy of the respiratory tract.[11]

SUMMARY

1. The average internist, including those who specialize in chest diseases, has more or less neglected the field of allergy. He is apt to try to find the cause by history and clinical tests alone, and to disregard skin tests.

2. Skin tests, when properly carried out, and despite some minor limitations, are extremely valuable in discovering the cause or causes of allergic conditions, especially those of the respiratory tract.

3. Scratch tests should first be carried out, and then intracutaneous tests should be done when more information is necessary. We condemn those who use only one *or* the other technique.

4. Physicians who are not equipped to carry out skin tests should refer their allergic patients to an allergist who will make the allergy survey, and who will return the patient, if desired, with full instructions as regards avoidance of causative factors, and with solutions and dosage schedules if hyposensitization is necessary.

RESUMEN

1. Habitualmente, los internistas, aún los que se especializan en enfermedades del tórax, descuidan más o menos el campo de la alergia. Se inclinan más a buscar las causas por la historia clínica y por las pruebas clínicas, y pasan por alto las pruebas cutáneas.

2. Las pruebas cutáneas, cuando se hacen bien, a pesar de algunas limitaciones de menor importancia, son extremadamente valiosas para descubrir la o las causas de los padecimientos alérgicos, en particular los de las vías respiratorias.

3. Primero deben hacerse las pruebas con erosión cutánea y después las reacciones intracutáneas cuando se necesita una información más. Nosotros condenamos el uso de sólo una o la otra técnicas.

4. Los médicos que no están equipados para realizar las pruebas cutáneas deben enviar sus enfermos al alergista quien hará la investigación alérgica y devolverá el enfermo si así se desea con instrucciones completas en lo que respecta a evitar las causas así como dará las soluciones y dosificaciones para obtener las hiposensibilización si se necesita.

RESUME

1. Dans l'ensemble le médecin, y compris celui qui se spécialise dans les affections thoraciques, néglige plus ou moins le domaine de l'allergie. Il est susceptible de tenter de rechercher la cause par l'histoire de la maladie et les seuls éléments cliniques, mais a tendance à mépriser les tests cutanés.

2. Les tests cutanés, lorsqu'ils sont pratiqués avec soin, et malgré quelques contraindications mineures, sont du plus haut intérêt pour découvrir la cause des états allergiques, particulièrement ceux des voies respiratoires.

3. On doit d'abord essayer les cuti-réactions et ensuite s'il est nécessaire d'avoir des renseignements complémentaires, on peut pratiquer des épreuves intradermiques. Les auteurs n'admettent pas que l'on utilise seulement l'un ou l'autre de ces procédés.

4. Les médecins qui ne sont pas équipés pour pratiquer des tests cutanés devraient adresser leurs malades allergiques à un spécialiste qui effectuera la recherche de l'allergie, et qui renverra le malade avec les instructions qui permettront d'éviter les causes déclenchantes, ainsi que les conseils thérapeutiques si la désensibilisation est nécessaire.

ZUSAMMENFASSUNG

1. Der durchschnittliche Internist einschliesslich eines solchen, der sich für Thoraxerkrankungen spezialisiert, hat das Gebiet der Allergie mehr oder weniger vernachlässigt. Er neigt dazu, die Krankheitsurachen aus Vorgeschichte und klinischen Untersuchungen allein zu ermitteln und Haut-Teste auseer acht zu lassen.

2. Werden Hautproben richtig ausgeführt, so sind sie trotz einiger unbedeutender Einschränkungen von ausserordentlichem Wert für Feststellung der Ursache oder Ursachen allergischer Krankheitsbedingungen, vor allem solcher des Respirationstraktes.

3. Als erstes soll man Kratz-Teste ausführen und dann intrakutane Teste vornehmen, wenn genauere Information erforderlich ist. Wir missbilligen diejenigen, die nur von der einen oder der anderen Technik Gebrauch machen.

4. Ärzte, die nicht über die Ausrüstung verfügen, um Hautproben auszuführen, sollten ihre allergischen Patienten an einen Spezialisten für Allergie überweisen, der, falls es gewünscht wird, die Patienten zurückschicken wird mit genauen Angaben hinsichtlich der Vermeidung ursächlicher Faktoren und mit Arzneimittellösungen und Dosierungsplänen, falls eine Desensibilisierung notwendig ist.

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Tuberculosis in Hospital Employees as Affected by an Admission Chest X-ray Screening Program*

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For centuries the danger of contracting tuberculosis has been recognized as an occupational hazard for those engaged in the care of the sick. It is said that Valsalva (1666-1723) and Morgagni (1682-1771) avoided autopsies of those dying from phthisis for fear of contracting the disease and that Laennec (1789-1826) who died from tuberculosis, was convinced that he had acquired the disease while doing post-mortem examinations. In 1889, Cornet found that 63 per cent of all deaths among nursing nuns in Germany was due to tuberculosis.[1] The seriousness of the situation led J.A. Myers in 1930[2] to warn that, "It is obvious that under existing conditions the nursing care of the tuberculous is hazardous. The student nurse and the medical student should know that their professions are hazardous when they enter them"; and again in 1933[3] to admonish, "the incidence of tuberculosis among students and recent graduates of schools of nursing and medicine is so high that the disease may be looked upon as a serious menace to professional health workers."

Until comparatively recently, efforts to combat this hazard have been directed primarily towards preventing the spread of the disease from the known case of tuberculosis. However, in the past few decades those concerned with tuberculosis control have come to realize that perhaps an even greater source of infection was the patient with unsuspected tuberculosis on the general medical wards. It has been shown that in this group the disease might be 10 times as prevalent as in the general population.[4] As early as 1935, Myers proposed, among other measures taken to reduce the danger of infection, that a chest roentgenogram should be obtained of each patient admitted to the hospital.[5]

The purpose of this paper is to evaluate the effectiveness of a routine admission chest x-ray screening program in reducing the incidence of tuberculosis in the personnel of a large general hospital.

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*A portion of this material was presented in a panel discussion before Section on Diseases of the Chest, 105th Meeting of American Medical Association, Chicago, Illinois, June 13, 1956.

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Tuberculosis in Hospital Personnel

Since the latter part of the nineteenth century a great many papers have been published dealing with all phases of the problem of tuberculosis in hospital personnel. The literature to 1950 has been summarized in a number of excellent reviews.[5, 6, 7, 8, 9] Most authors have agreed that the morbidity and mortality of tuberculosis in internes, medical students and nurses has been appreciably higher than other comparable non-exposed groups, with some estimating it to be five or six times as great. However, though she was of the same opinion, Connolly in 1950[9] cautioned that there were really few adequate studies, and that of these, almost all were made prior to 1945 and most prior to 1940. In addition, they were concerned mainly with tuberculin conversion. More recently a number of studies have been published dealing with the incidence of active tuberculosis in hospital employees.

TABLE I

TUBERCULOSIS IN LOS ANGELES COUNTY HOSPITAL EMPLOYEES
Interval Between Last Negative and First Positive Chest Roentgenogram

Interval In Years	Cases
0 - 1	35
1 - 2	20
3 - 4	3
5 - 9	2
10 and over	1
Total Available	61
No positive roentgenogram	3
No previous roentgenogram	26
TOTAL	90

TABLE II

TUBERCULOSIS IN LOS ANGELES COUNTY HOSPITAL EMPLOYEES
Extent of Disease

	Cases
Minimal	53
Moderately advanced	16
Far advanced	5
Pleural effusion	7
Other	5
Unknown	4
TOTAL	90

Childress[10] reported his finding for the years 1932 to 1951 for a small general hospital. In those employees exposed to tuberculous patients the incidence rate was 6.6 cases per 1,000 person years, and for non-exposed personnel, 1.3 per 1,000 person years. He compared these rates to that of employees of the Metropolitan Life Insurance Company, 0.2 to 0.3 per 1,000 person years.

In 1951, Katz, Plunkett, and MacCurdy[11] published a detailed study of 14 institutions for the mentally ill. They considered a case of newly developed tuberculosis to be one in which there was a positive chest roentgenogram following a previously negative one. A case was not accepted when only the initial film was positive. In these hospitals, they found an over-all case rate of 1.1 per 1,000 person years while in employees of state schools the rate was only 0.31. The rate of infection among the employees on the tuberculosis wards was 7.43 as compared to 0.83 for employees on the non-tuberculosis wards. They reported no significant difference in the rates of attendants, nurses and physicians.

In 1952, Mikol, Horton, Lincoln and Stokes[12] reported an incidence rate of 9.1 cases per 1,000 person years in three state tuberculosis hospitals. They estimated this to be about nine times that of the population rate. Unlike Katz, et al., they demonstrated a difference in the infection rate of various categories of employees, i.e.: nurses, 20.9; technical employees, 12.3; ward dietary, 10.6; laundry, 8.7; and housekeeping, 7.4. No mention was made of physicians.

Riggins in 1953[13] studied the tuberculosis rate in student nurses and medical students in various sections of the United States. He showed that the morbidity rate varied with the community and concluded that "tuberculosis morbidity among nurses, medical students, certain internes,

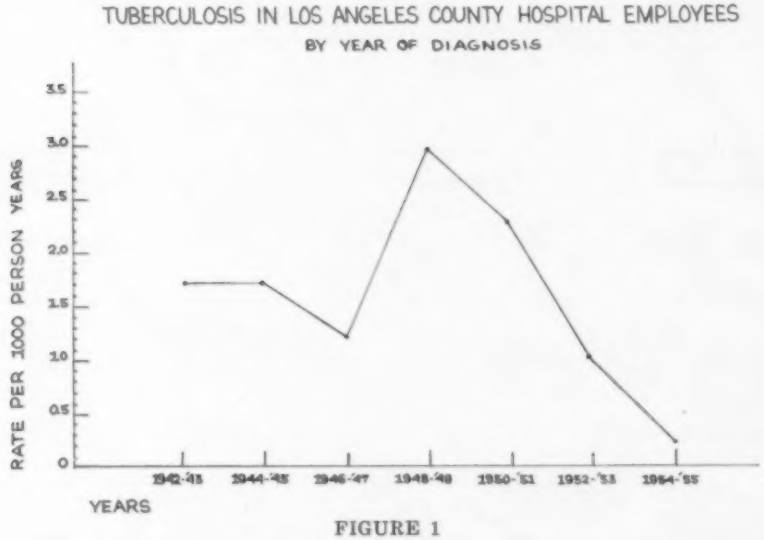

FIGURE 1

(laboratory workers) and other exposed young adults is frequently higher than for unexposed personnel within the hospital and for young adults having other occupations."

Tuberculosis in Los Angeles County Hospital Employees

From 1942 through 1955, a 14 year period, the California State Industrial Compensation Board compensated 90 employees of the Los Angeles County Hospital for tuberculosis on the basis that their hospital employment was a contributing factor in the development of their disease. This undoubtedly represents a minimum figure inasmuch as other cases probably occurred which were not recognized or recorded through the filing of claims. Since the time between exposure to tuberculosis and the appearance of recognizable disease is so variable, a number of employees who developed their tuberculosis less than six months after coming to work in the hospital were arbitrarily excluded from this study.

Previously negative chest roentgenograms were available before the discovery of tuberculosis in two-thirds of these employees (Table I). In most of these, the interval between the last negative roentgenogram and the first positive one was less than one year and in only a few instances was it greater than two years. An earlier roentgenogram was not available in 26 of the cases and it might be properly argued that there was no definite proof that these individuals had contracted their tuber-

TABLE III

TUBERCULOSIS IN LOS ANGELES COUNTY HOSPITAL EMPLOYEES
Bacteriology

	Cases
Sputum positive	45
Sputum negative	12
Unknown	33
TOTAL	90

TABLE IV

TUBERCULOSIS IN LOS ANGELES COUNTY HOSPITAL EMPLOYEES
Course of Disease

	Cases
Regressed	27
Unchanged	5
Progressed	2
Died	5
Unknown	51
TOTAL	90

culosis at the hospital. However, a majority of these had been employed for more than three years and most had minimal or obviously acute disease. In three instances no positive chest roentgenograms were ever obtained; two of these patients were student nurses with sputum-positive primary tuberculosis; and the third was a physician with a tuberculous salpingitis.

Three-fourths of these patients were women, more than one-half of whom were under 35 years of age, and one-fourth were under 25. Among the men, there were none under 25 years of age, though the average was below 40. More than one-half of the patients were Caucasians and about one-third were Negroes. Notably there were only four Latin Americans. However, no comparisons can be made since the distribution by age, race and sex of all hospital employees for this period is not known.

The extent of the disease at the time of its detection is indicated in Table II. The majority of patients had minimal tuberculosis, though there were some with moderately advanced and, in a few instances, even far-advanced disease. Others were diagnosed as having primary, miliary, or extrapulmonary tuberculosis.

In the majority of cases the diagnosis of tuberculosis was conclusively established by positive bacteriologic findings (Table III). Unfortunately (Table IV) no follow-up information could be obtained for most of the patients. In most of those for whom such information is available, the disease is known to have been regressed. However, five are known to have died of their tuberculosis.

The number of cases diagnosed each year between 1942 and 1955 is shown in Table V. No earlier figures are included because the records of patients awarded compensation prior to this date could not be obtained.

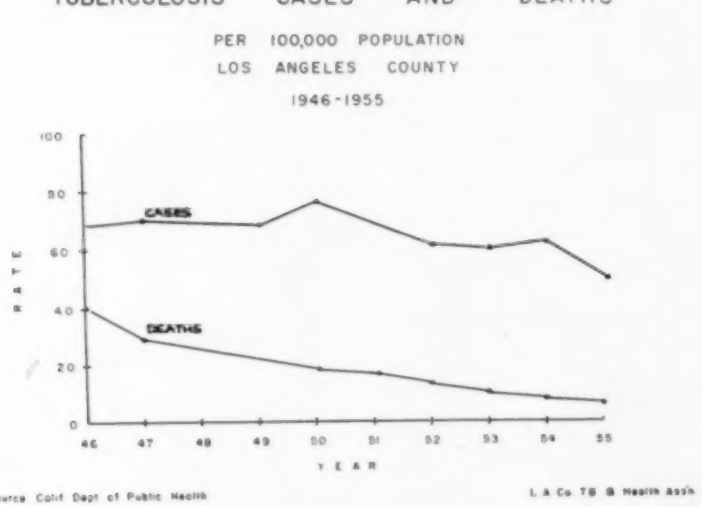

FIGURE 2

Also there were undoubtedly more cases in 1946 than indicated since complete records for this year were also unobtainable. The incidence has been expressed as rate per 1,000 person years of exposure rather than rate per total individuals exposed because the exact number of individuals employed in a given year in any one position is not known. In addition, the period of employment varies greatly; some have worked only a few weeks or months while others have remained for many years.

The incidence rate (Fig. 1) was fairly constant from 1942 (1.3 per thousand person years) to 1947 (1.8 per thousand person years) but rose sharply between 1948 and 1950 to a maximum of 3.3 per thousand person years in 1949. This rise was probably in large part due to the case finding activities undertaken by the United States Public Health Service at about that time and the county-wide mass chest survey which took place in 1950. In 1951 the rate returned to the 1947 level.

In October, 1951 the routine admission chest x-ray screening program of the hospital was begun. Since the early part of 1952, a yearly 70 mm. photofluorogram has been obtained of each employee with nurses, physicians and employees on the tuberculosis wards being examined semi-annually. Prior to 1952, only physicians, student nurses and tuberculosis employees were examined regularly. The incidence rate showed a definite drop in 1952 and 1953, and in 1954 and 1955 declined abruptly to 0.2 and 0.4 cases per thousand years of exposure respectively (Table V).

TABLE V

TUBERCULOSIS IN LOS ANGELES COUNTY HOSPITAL EMPLOYEES
Year in Which Disease Was Diagnosed

Year	Cases	Person Years	Rate*
1942	4	3,142	1.3
1943	6	2,834	2.1
1944	5	3,329	1.5
1945	7	3,681	1.9
1946	3	3,952	0.8**
1947	7	3,822	1.8
1948	11	4,205	2.6
1949	15	4,474	3.3
1950	12	4,480	2.7
1951	8	4,412	1.8
1952	5	4,552	1.1
1953	4	4,478	0.9
1954	1	4,546	0.2
1955	2	4,653	0.4

*Rate per 1,000 person years.
**Records for this year incomplete

A little more than one-half of the cases occurred during the first three years of employment (Table VI). This should not be interpreted as meaning that the infection rate is necessarily higher during this period for it is also the time during which there is the greatest turnover of employees. In most categories of employees, this averages approximately one-third each year. Internes are usually exposed for one year, and resident physicians and student nurses are exposed for a maximum of three years. The decrease in the number of cases with increasing exposure years is probably proportional to the employees involved.

The year in which each individual who developed tuberculosis was employed is shown in Table VII. An average of eight cases per year developed in those employed between 1939 and 1948 with no significant variation from year to year. This decreased to three cases for those employed in 1949 and four cases for 1950 employees. There was a further reduction to two cases per year for those employed in 1951 and 1952. To date, though more than three years have elapsed, no one employed since 1952 has developed tuberculosis. This is particularly significant when it is recalled that previously the greatest number of cases have developed during the first three years of employment.

Only one-third (31) of the group indicated that they had been employed on the tuberculosis wards at any time (Table VIII). Nine employees (10 per cent) who were clerical, maintenance and janitorial personnel had no close patient contact, while the remainder, almost 60 per cent, worked on either the general wards or in the laboratories.

The importance of the degree of exposure is further emphasized by Table IX. From 1942 through 1951, the incidence rate for all personnel was 2.0 cases per 1,000 person years of exposure, and the rate for

TABLE VI

TUBERCULOSIS IN LOS ANGELES COUNTY HOSPITAL EMPLOYEES
Duration of Employment

Years of Exposure	Cases
½ - 1	12
2 -	18
3	18
4	7
5	7
6	9
7	4
8	1
9	3
10 and over	11
TOTAL	90

exposed personnel was 3.2 as compared to 0.5 for non-exposed personnel or six times as high. The incidence rate among physicians was 5.7, nurses 2.4, and ward attendants 3.2. The highest rate, 13.0, was encountered among laboratory technicians and morgue attendants.

The routine admission chest x-ray screening program which was instituted in the latter part of 1951 resulted in the early recognition and isolation of tuberculosis patients and reduced exposure of ward personnel. It may be assumed that the educational effects of this screening program also led to greater caution in the handling of known tuberculous patients. During the first two years of the chest x-ray screening program, the over-all rate as well as the rate for the exposed and non-exposed groups was cut in half. From 1954 through 1955, the rate for all personnel was reduced further to 0.3 and the rate for the exposed group to 0.6 cases per 1,000 person years. No cases occurred among the non-exposed personnel, physicians or nurses. Two ward attendants and one laboratory technician were the only employees to develop tuberculosis during these two years. It is interesting that two of these employees had worked on the tuberculosis wards for years and the third employee had a known outside contact. There was only one instance of tuberculosis in a physician during the four years from 1952 through 1955. This occurred in January, 1952, soon after the admission chest program was begun,

TABLE VII

TUBERCULOSIS IN LOS ANGELES COUNTY HOSPITAL EMPLOYEES
Year of Employment

Year	Cases
1939	9
1940	5
1941	9
1942	6
1943	5
1944	5
1945	9
1946	11
1947	13
1948	7
1949	3
1950	4
1951	2
1952	2
1953	0
1954	0
1955	0

whereas there were 12 cases in the preceding 10 years.

The sharp decline in the incidence rate beginning in 1952 is too marked to be dismissed as mere coincidence or as an expression of the decrease of tuberculosis in the general population. While deaths due to tuberculosis have continued to decline rather spectacularly, there has been no comparable decrease in the incidence of the disease. The new active case rate for Los Angeles County (Fig. 2) has remained fairly stable since 1946, though it did show a significant drop in 1955, possibly reflecting at last the case finding efforts of the community and the diminishing death rate.

The isolation of and the prevention of exposure to the unsuspected cases of tuberculosis uncovered by the admission chest x-ray screening program has been the principal factor in the dramatic and almost complete eradication of the disease in personnel working on the general

TABLE VIII

TUBERCULOSIS IN LOS ANGELES COUNTY HOSPITAL EMPLOYEES
History of Exposure Within Hospital

	Cases	Per Cent
Tuberculosis Wards	31	34
Laboratory (including Mortuary)	9	10
General Wards	41	46
No Close Patient Contact	9	10
TOTAL	90	

TABLE IX

TUBERCULOSIS IN LOS ANGELES COUNTY HOSPITAL EMPLOYEES
By Occupation and Relation to Beginning of Admission Chest X-Ray Screen Program in October 1951

	1942 - 1951			1952 - 1953			1954 - 1955		
	Cases	Person Years	Rate*	Cases	Person Years	Rate*	Cases	Person Years	Rate*
Exposed Personnel									
Physicians	12	2,118	5.7	1	572	1.7	0	587	0.0
Nurses	30	12,585	2.4	4	2,782	1.4	0	2,774	0.0
Ward Attendants	20	6,278	3.2	2	1,601	1.2	2	1,515	1.3
Laboratory Technicians and Morgue Attendants	8	614	13.0	1	156	6.4	1	167	6.0
Subtotal	70	21,595	3.2	8	5,111	1.6	3	5,043	0.6
Non-exposed Personnel	8	16,736	0.5	1	3,919	0.3	0	4,156	0.0
TOTAL	78	38,331	2.0	9	9,030	1.0	3	9,199	0.3

*Rate per 1,000 person years.

wards of the Los Angeles County Hospital. Added precautions in caring for the known tuberculous patients have produced almost equal results among the employees on the tuberculosis wards. Two individuals who began to work in the hospital during the first year of the admission chest x-ray program have developed tuberculosis; one was a vocational nurse on a tuberculosis ward, and the other was a student nurse who developed a minimal lesion just a few months after the program had begun. Not one instance of tuberculosis is known to have developed in a person employed in the following three years, a period during which, it has been our experience, the greatest number of cases could be expected. Employees at other units of the Los Angeles County Hospital system, where conditions are much the same as at our hospital except that there are no admission chest x-ray programs, continue to develop tuberculosis.

It has been estimated that the direct cost of caring for a case of tuberculosis has been from $10,000 to $15,000 though at present this may be somewhat less due to advances in therapy. The prevention of numerous cases of tuberculosis by the admission chest x-ray screening program has resulted in savings of compensation funds alone which have much more than paid for the program, to say nothing of the hardships and economic loss spared the patient and his family.

SUMMARY

Tuberculosis represents a distinct occupational hazard to hospital employees. This danger has been attested by the fact that from 1942 through 1955, 90 employees of the Los Angeles County Hospital were awarded compensation for tuberculosis. Five of these patients are known to have died of their disease. The incidence was six times as high among those having close contact with patients: i.e., physicians, nurses, attendants, laboratory technicians, etc., as among clerical and other non-exposed personnel.

Since the institution of a routine admission chest x-ray screening program in the latter part of 1951, the danger of an employee contracting tuberculosis has almost disappeared. The incidence of newly developed disease among employees has dropped to less than one-fifth of the former rate and not one instance has been found so far among those who began to work at the hospital after 1952. The early recognition and isolation of patients with hitherto unsuspected tuberculosis on the general wards of the hospital should be emphasized as the most important means of reducing personnel exposure and infection.

The saving in compensation alone has already amounted to more than the cost of the entire admission chest screening program.

RESUMEN

La tuberculosis constituye un riesgo definido para los emplea dos de hospital. Este riesgo ha sido probado por el hecho de que des de 1942 hasta 1955, 90 empleados del Hospital del Condado de Los Angeles, obtuvieron compensación por tuberculosis. Se sabe que cinco de estos en-

fermos murieron de la enfermedad. La incidencia fué cinco veces más elevada que la de los que tienen contacto con los enfermos, como los médicos, enfermeras, ayudantes, técnicos de laboratorio. etc.. así como entre otros empleados no expuestos.

Desde que se ha instituído el examen de rutina a los rayos X para la admisión en las postrimerías de 1951, el peligro de que los empleados contraigan tuberculosis casi ha desaparecido. La incidencia de la enfermedad nueva desarrollada entre los empleados hacaído a menos de un quinto de lo que antes había y no se ha encontrado un solo caso entre los que empezaron a trabajar en el hospital después de 1952.

El descubrimiento temprano y el aislamiento de los enfermos con tuberculosis hasta entonces insospechada que se encuentren en las salas generales, debe ser recalcado, como el medio más importante para reducir la exposición del personal a la infección.

La economía en gastos de compensación por sí sola ha sido más grande que el costo de todo el programa de descubrimiento entre los casos de nueva admisión.

RESUME

La tuberculose reprèsente un risque professionnel distinct pour les différents employés d'un hôpital. Ce danger se matérialise par le fait que de 1942 à 1955, 90 employés de l'hôpital du district de Los Angeles eurent droit à une indemnité pour tuberculose. Cinq de ces malades sont morts de leur affection. La fréquence des atteintes fut six fois plus élevée parmi ceux qui étaient en contact étroit avec des malades, c'est-à-dire les médecins, infirmières, assistants, techniciens de laboratoires, etc., que parmi les religieux ou les autres membres du personnel non exposés.

Depuis l'institution d'un contrôle radiologique systématique à l'embauche dans la dernière partie de l'année 1951, le danger de contamination pour l'employé a presque disparu. La fréquence des atteintes apparues récemment chez les employés est tombée à mois de 1/5 du taux ancien, et aucun cas n'a été découvert parmi ceux qui ont commencé à travailler à l'hôpital après 1952. On devrait insister sur le dépistage précoce et l'isolement des malades atteints de tuberculose jusque là insoupçonnée dans les services généraux de l'hôpital comme moyens les plus importants de réduire le risque et l'infection.

L'économie faite seulement sur l'octroi des indemnités a déjà atteint plus que le coût de la totalité des frais nécessités par le contrôle radiologique avant embauche.

ZUSAMMENFASSUNG

Die Tuberkulose stellt ein ausgeprägtes berufliches Wagnis dar für Krankenhaus-Angestellte. Diese Gefahr wurde bezeugt durch die Tatsache, dass von 1942 bis Ende 1955 90 Angestellten des Kreiskrankenhauses von Los Angeles eine Entschädigung wegen Tuberkulose zugesprochen worden ist. Von 5 dieser Kranken ist bekannt, dass sie an ihrer Erkrankung gestorben sind. Die Krankheitshäufigkeit war 6mal höher bei denjenigen, die einen engen Kontakt mit Patienten gehabt hatten, d.h. Ärzten,

Schwestern, Wärtern, Laborangestellten usw. als bei geistlichem und anderem nicht exponierten Personal.

Seit der Einführung des planmässigen Thorax-Röntgenschirmbild-Programmes bie Krankenhauseintritt gegen Ende 1951 ist die Gefahr einen Angestellten, sich eine Tuberkulose zuzuziehen, fast ganz geschwunden. Das Vorkommen einer sich neu entwickelnden Erkrankung unter Angestellten ist auf weniger als 1/5 der früheren Ziffer zurückgegangen, und bisher ist noch kein Fall gefunden worden bei denjenigen, die nach 1952 ihre Arbeit im Krankenhaus aufnahmen. Die frühzeitige Feststellung und Isolierung von Kranken mit bis dahin nicht vermuteter Tuberkulose auf den allgemeinen Stationen der Krankenhäuser muss als das wichtigste Verfahren herausgestellt werden, um die Exposition und Infektion des Personals zu verringern.

Die Einsparung allein an Entschädigungen hat bereits die Kosten des gesamten Thorax-Schirmbild-Verfahrens bei Krankenhauseinweisung übertroffen.

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The Surgeon and Cardio-pulmonary Physiology

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The day has arrived in cardio-pulmonary surgery when the surgeon can no longer rely entirely on his clinical acumen and visual radiological impression in assessing the status of a patient. Cardio-pulmonary function tests now play a definite role both in the preparation of a patient for surgery and in following post-operative progress.

An exact method has now been developed to determine the normal lung compartments to within an error of 0.70 per cent.[1] By this method small deviations in residual volume (RV) can be measured and the surgeon can easily follow the changing status of a patient with, for example, mitral stenosis. If the heart is normal in size the pulmonary capillary pressure (PC) and mean pulmonary artery pressure (PA) vary directly with the residual volume.[2] Any increase in the residual volume indicates a worsening of the physiological effects of the stenosis. If the heart is grossly enlarged however, the residual volume will be diminished by an amount commensurate with the cardiac enlargement (vide infra).

In the differential diagnosis of constrictive pericarditis and mediastinitis, superior vena cava fibrosis and pulmonary fibrosis with or without emphysema (Hamman-Rich or others), the physiological knowledge of the surgeon is heavily drawn upon since it is he who must make the final decision.

In order to investigate the status of a patient from the physiological standpoint of importance to the surgeon, the vital capacity (VC) and residual volume are determined in the usual manner. From a single inspiratory posteroanterior x-ray film the true total lung capacity is calculated.[1] This determines the exact predicted residual volume for that particular person. Since normally a definite percentage of the total lung volume (TC) is residual volume the individual's deviation will now be apparent.[3] Whenever one wishes to reassess the patient's status these studies are repeated.

The volume of the heart is calculated as a paraboloid of revolution.[1] The changes in its volume can be noted by calculation from repeated x-ray films. If its volume increases, the amount of the increase is to be subtracted from the previous residual volume as calculated before this increase to give the present residual volume corrected for changes in the heart size per se, (and vice versa if the heart volume decreases). The change in heart volume will of course be reflected in the TC volume change. The reassessed present residual volume will be equal to this previous residual volume corrected as stated above for any change in

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heart volume if there has been no change in the physiological status of the patient other than merely the change (increase or decrease) in the heart volume. If there has been a true physiological improvement this corrected residual volume will be less than before while if the patient is deteriorating it will be higher. For example effective therapy and/or diuretics will lessen this residual volume while an increase in PC pressures will augment the residual volume corrected for any coincidental change in the heart size.

Case 1: F. F., a man aged 47 years, is an example of the point under discussion and also illustrates another point. He was admitted for reoperation of a mitral valve. Before his first operation he had such severe haemoptysis as to require many repeated transfusions. On his present admission he was dyspnoeic at rest, showed the muscle wasting of advanced mitral stenosis and suffered from extreme fatigue. There was marked cardiac enlargement of both ventricles especially the left. His VC, RV and TC preoperatively were 1672, 3796 and 5486 ml. respectively. The TC is approximately normal but his RV is 2200 ml. above normal (+ 240 per cent) indicative of a severe change in pulmonary hemodynamics.[2] After four minutes of bronchodilator aerosol his VC increased 220 ml. and his maximum breathing capacity (MBC) increased by 14 litres per minute. This is indicative of an "occult pulmonary oedema" (there was no question of bronchospastic disease in this patient).

A month later when his clinical status seemed unchanged his VC, RV and TC were 1310, 4063, 5373 ml. The 267 ml. increase in RV represents a worsening in his physiological status because the failing left ventricle is causing more back pressure and an increased PC pressure, in the presence of a sustaining right ventricle and a slight progression of pulmonary small artery muscular hypertrophy and fibrosis.[4] The 95 ml. decrease in TC is indicative of a slight pulmonary oedema. Bronchodilator aerosol confirms this by showing an increase of 138 ml. in his VC and of 14 1/min. in his MBC.

An attempt at refracturing his mitral valve through the left inferior pulmonary vein was unsuccessful. For about three weeks post-operatively he had clinical pulmonary oedema. His VC and RV and TC were now 1400, 2099 and 3499 ml. respectively. The decrease in TC of 1960 ml. is due to frank pulmonary oedema which at first affects the residual volume, but not the vital capacity, at least not until the residual air is "used up" so to speak. The size of the heart did not change during the studies.

Case 2: R. T., a man aged 36 years, who has mitral stenosis, illustrates the converse. He was inducted into the United States Army and recently served three years on active duty. Asymptomatic, his VC was 3840, and his RV was 1705 ml. both relatively normal values.

Consider now a problem of combined surgical and medical heart and lung pathology such as was mentioned in the introduction of this communication and to illustrate this the following case is presented.

Case 3: J. E., a 47 year old woman, was diagnosed clinically as having emphysema, pulmonary fibrosis, cor-pulmonale and constrictive pericarditis. Her VC and MBC were 1430 (normal 3000) ml. and 22 (normal 90) litres per minute which did not increase with a bronchodilator. Her residual volume was 1686 (normal 1600) ml. or 46 per cent of her TC of 3116 ml. The TC was 65 per cent of normal. Her alveolar N_2 was 1.83 per cent, O_2 removal was 33 (normal 43) and 43 (normal 63) ml. per litre at rest and exercise.

Cardiac catheterization studies showed a RAm pressure of 2, PAm of 40, pulmonary artery pressure S/D of 50/35, PC pressure of 8 mm. Hg. haemoglobulin saturation of 83 per cent, arterial CO_2 of 49.5 vols. per cent, cardiac index of 3.61 L./m^2 and an A-V O^2 difference of 5.9 vols. per cent. Cardiac catheterization ruled out constrictive mediastinal pericarditis (the right ventricle dicrotic wave was normal in its contour),[5] and proved pulmonary artery hypertension in the presence of a normal PC pressure.

Pulmonary function studies ruled out emphysema and proved interstitial fibrosis on the basis of a normal alveolar nitrogen and timed vital capacity and diminished total lung capacity with a relative (not absolute) increase in the RV.[6]

There is a normal cardiac output, but diminished O_2 removal at rest and exercise. These findings indicate that there is an impairment of O_2 diffusion similar to the "alveolocapilliary" block syndrome of diffuse miliary metastatic pulmonary carcinoma from breast cancer or Hamman-Rich's disease; the haemoglobin saturation confirms it.[7] This can be inferred without catheterization studies from the lung function studies alone.

Consider the physiology of the "vanishing lung" or localized emphysema from the standpoint of the surgeon.[8, 9, 10]

Case 4: S.P., a 52 year old man, who was admitted with the diagnosis of bilateral large cysts of the upper lobes, presented the problem as to the feasibility of removal, and if so should both sides be done at once? He also had pulmonary osteoarthropathy. The pulmonary ventilation findings were as follows: VC 2330, expiratory capacity 650, RV 4915, TC 7245 ml., MBC 42 l/min., ventilation at rest 6.6 l/min., ventilation on exercise 11 l/min., O_2 cons. 222 at rest and 370 ml./min. on exercise. Resting O_2 removal was 34 ml./l and the same on exercise, alveolar N_2 was 6.5 per cent. Angiocardiography showed no perfusion of either lobe. The haemoglobin saturation was 95 per cent, brachial artery O_2 18.1 vols. per cent and Co_2 42.5 vols. per cent. Cardiac findings were not significant. Since CO_2 is 25 times more diffusable than O_2[11] and since his blood CO_2 is below normal he is physiologically able to excrete all his CO_2 and it is being excreted into an area where the level of CO_2 is subnormal, not into the cystic area, and then out through the bronchii. This means that the cysts are merely space occupying lesions, non-perfused and only partially ventilating since the O_2 removal is not excessively reduced below the normal 40 ml./l. Surgery will benefit this patient because it will remove the useless partial ventilation of a non-perfused "lung zone." There is a relative over ventilation and over perfusion of the lower two lobes to prevent anoxia which results in an excess CO_2 "blow off" with its accompanying low arterial blood CO_2. Along with this there is, of course, a lowered plasma $Na+$ due to renal compensation and decreased total ionic plasma osmolarity.[12]

Discussion

It is necessary to digress into the pathologic physiology of the alveolus in mitral stenosis to understand the significance of changes in the residual volume. The normal diameter of an alveolus is from 12-24 microns. In mitral stenosis this diameter increases to from 20-50 microns. Since there is rigid mathematical proof that of all isoperimetric figures that which contains the greatest area is a circle, it follows that the integral (using it in its true mathematical sense) of large spheres is greater than the integral of small spheres.[13] The increase in the size of the individual sphere (alveolus) is due to a rounding out of the alveolar capillaries due to the increase in PC pressure from back pressure of the stenosis. In mitral stenosis therefore one finds an increase in the residual volume.

Enlargement of the heart per se decreases the residual volume by displacing residual air. Frank clinical pulmonary oedema of course, diminishes residual volume by actually replacing the air with transudate.[2]

There is another phenomenon which must be commented upon. Some patients with heart disease (and neither asthma nor emphysema) will show a definite increase in their vital capacity after a bronchodilator. These patients do not have clinical pulmonary oedema but may be said to have an "occult pulmonary oedema" which reveals itself in this manner.[2] The post-operative progress of a patient subjected to any thoracic procedure can be accurately followed by cardio-pulmonary tests. For example in assessing the value of diamox and other diuretics in the preparation of the patient for cardiac surgery pulmonary function tests play a definite role. Diuresis results in a diminution of the extracellular fluid in the alveolocapillary membrane. This in turn causes an increase in flexibility of this membrane (a change in the compliance of the system), which manifests itself as an increase in vital capacity together with a corresponding decrease in the residual capacity. There is a change in "dead non-functioning" residual air to utilizable vital air.

Pulmonary function tests can now play a definite role in both preparation of a patient for surgery and in following the post-operative progress.

SUMMARY

Cardio-pulmonary function studies of patients have now come to maturity. An accurate method of predicting the normal lung compartments for a particular patient has been devised. Deviations from this are significant.

Mitral stenosis results in an increase in residual volume and this is directly proportional to the extent of the functional impairment, the pulmonary capillary pressure and the mean pulmonary artery pressure.

In patients with "litre" hearts the large heart of itself displaces residual air and the augmented residual volume is then reduced by an amount commensurate with the enlargement.

The progress of a disease such as mitral stenosis and the effect for example of surgery can be assessed by repeated residual volume determinations which are devoid of psychogenic factors.

Occult pulmonary edema is revealed by vital capacity and maximum breathing studies before and after the use of a bronchodilator aerosol where increases in both occur.

Frank pulmonary edema decreases the residual volume first and then the vital capacity.

Constrictive mediastinal pericarditis is shown by cardiac catheterization as a notch on the right ventricle dicrotic wave.

Diseases with pulmonary fibrosis can be differentiated from emphysema by a decreased total lung capacity and a relatively normal alveolar nitrogen, timed vital capacity and residual volume.

A diminished oxygen removal at rest and exercise occurs in the alveolo-capillary block syndrome even if the hemoglobin saturation is normal. It also occurs where there is impaired perfusion of a lung or parts of a lung because of vascular obstruction or impaired cardiac output. It remains low on exercise if the defect is fixed such as occurs in malignant involvement of the pulmonary artery. If the neoplasm is operable it does not interfere with the pulmonary blood flow and the O_2 removal is normal at rest and increases on exercise.

Cardio-pulmonary function studies before and after exercise determine the finiteness of thoracic surgery. Angiocardiography shows perfusion changes in the lungs. Brachial artery gas analysis indicates hyperventilation with decreased CO_2 and decreased pulmonary diffusability if the oxygen content is low (and the heart normal). In bilateral lung cyst a low oxygen removal indicates ventilation of useless (nonperfused) lung zone.

In mitral stenosis the alveolar diameter is doubled due to an increased pulmonary capillary pressure which in turn reflects itself as an increased residual volume.

RESUMEN

Los estudios de la función cardiopulmonar en los enfermos, han llegado a su madurez. Se ha ideado un método exacto para predecir la función de los segmentos pulmonares en un enfermo determinado. Las desviaciones de esto son significativas.

La estenosis mitral da por resultado un aumento del volumen residual y esto es directamente proporcional a la magnitud del daño funcional, la presión capilar normal y la media de presión de la arteria pulmonar.

En los enfermos con corazón crecido (corazón de un "litro") el corazón grande por sí mismo desplaza el aire residual y el aumento del volumen residual es reducido en una proporción relacionada con el crecimiento cardiaco.

La evolución de una enfermedad tal como la estenosis mitral y el efecto por ejemplo, de la cirugía, pueden estimarse por repetidas determinaciones del volumen residual en las que se excluyen los factores psicógenos.

El edema pulmonar oculto se revela por los estudios de la capacidad vital y la respiratoria máxima antes y después del uso de los aerosoles broncodilatadores cuando aumento en ambos ocurre.

El edema pulmonar franco disminuye primero el volumen residual y después la capacidad vital.

La pericarditis mediastinal constrictiva se muestra por la cateterización cardiaca como una muesca sobre la onde dicrótica del ventrículo derecho.

Las enfermedades con fibrosis pulmonar pueden diferenciarse del enfisema por un decrecimiento total de la capacidad pulmonar y relativamente normal nitrógeno alveolar, capacidad vital en razón del tiempo, y volumen residual.

Una disminuída absorción de oxígeno en deposo y en ejercicio se observa en el bloqueo alveolocapilar aún si la saturación de oxígeno es normal. También ocurre así cuando hay deficiente perfusión de un pulmón o de partes de él a causa de obstrucción vascular o por deficiente rendimiento cardiaco. Permanece bajo en el ejercicio si se ha fijado el defecto como ocurre cuando hay invasión maligna de la arteria pulmonar.

Si la neoplasia es operable no interfiere con el flujo sanguíneo pulmonar y la absorción de O2 es normal en reposo y aumenta con el ejercicio.

Los estudios cardio-pulmonares antes y después de ejercicio determinan las limitaciones de la cirugía torácica. La angiocardiografía muestra los cambios de perfusión en los pulmones.

Los análisis de gases de la arteria braquial indican la hiperventilación con disminuído CO2 y el decrecimiento de la difusibilidad si el contenido de oxígeno es bajo (y el corazón normal).

En los quistes pulmonares bilaterales, la absorción baja de oxígeno indica que la ventilación (Falta de perfusión) en las zonas pulmonares inútiles.

En la estenosis mitral el diámetro se dobla debido a un aumento de la presión pulmonar capilar que a su vez se refleja en un aumento del volumen residual.

RESUME

Les études de la fonction cardiopulmonaire des malades sont maintenant bien au point. Une méthode précise pour établir le standard du poumon normal chez un malade a été mise au point. Les anomalies prennent leur valeur par rapport à cette référence.

La sténose mitrale provoque une augmentation du volume résiduel et ceci est directement proportionnel à l'étendue du trouble fonctionnel, à la pression de l'artère et des capillaires pulmonaires.

Chez les malades atteints de coeur hypertrophique, le coeur déplace de lui-même l'air résiduel et le volume résiduel augmenté est alors réduit par un volume proportionné à l'augmentation cardiaque.

L'évolution d'une affection telle que la sténose mitrale et l'effet de la chirurgie par exemple, peuvent être déterminés par des examens répétés du volume résiduel, qui sont indépendants de facteurs psychogéniques.

L'oedème pulmonaire occulte est révélé par des études sur la capacité vitale et la capacité respiratoire maximum avant et après l'emploi d'aérosol bronchodilatateur. Le taux est augmenté dans chacun de ces cas. L'oedème pulmonaire franc fait diminuer d'abord le volume résiduel et ensuite la capacité vitale.

La péricardite médiastinale constrictive est révélée par le cathétérisme cardiaque, qui montre une dépression sur l'onde dicrote du ventricule droit.

Les affections avec fibrose pulmonaire peuvent être différenciées de l'emphysème par la diminution de la capacité pulmonaire totale et un taux d'azote alvéolaire, une capacité vitale ainsi qu'un volume résiduel relativement normaux.

Une diminution de la fixation de l'oxygène au repos et à l'exercice survient dans le syndrome de bloc alvéolocapillaire même si la saturation en hémoglobine est normale. Elle survient aussi lorsqu'il y a une mauvaise irrigation du poumon ou d'une portion du poumon, par suite d'obstruction vasculaire ou de mauvais débit cardiaque. Elle reste faible à l'exercice, si le trouble est irréversible, tel qu'il survient dans les propagations de processus malins à l'artère pulmonaire. Si la néoplasie est opérable, il n'y a pas de troubles du débit pulmonaire sanguin, et la fixation de l'oxygène est normale au repos et augmente à l'exercice.

L'examen de la fonction cardiopulmonaire avant et après exercice fixe les limites de la chirurgie thoracique. L'angiocardiographie montre les altérations de la circulation sanguine dans les poumons. L'analyse du gaz à l'artère humérale indique l'hyperventilation avec diminution du gaz carbonique et diminution de la diffusion pulmonaire si le contenu oxygéné est faible et le coeur normal. Dans le cas de kyste pulmonaire bilatéral, une fixation d'oxygène faible indique la ventilation d'une zone pulmonaire sans fonction, parce que non irriguée.

Dans la sténose mitrale, le diamètre alvéolaire est doublé, grâce à une pression pulmonaire capillaire augmentée, qui à son tour se reflète dans une augmentation du volume résiduel.

ZUSAMMENFASSUNG

Cardiopulmonale Funktionsprüfungen an Patienten sind jetzt in ein Reifestadium eingetreten. Es ist eine genaue Methode zur Vorhersage der normalen Lungenleistungen für einen einzelnen Patienten aufgestellt worden. Abweichungen hiervon sind signifikant.

Die Mitralstenose hat eine Zunahme der Residualluft zur Folge, und dies ist direkt proportional der Ausdehnung der funktionellen Schädigung, dem pulmonalen kapillären Druck und dem mittleren pulmonalen Arteriendruck.

Bei Kranken mit "Liter"—grossem Herzen ver rängt das grosse Herz selbst die Residualluft und das erhöhte Residual-Volumen ist dann in einem der Vergrösserung entsprechendem Masse reduziert.

Das Fortschreiten einer Erkrankung so wie es die Mitralstenose ist, und die Wirkung beispielsweise der operativen Behandlung kann abgeschätzt werden durch wiederholte Bestimmungen der Residualluft-Menge, die frei von psychogenen Faktoren sind.

Ein Kultes Lungenoedem wird offenbar durch die Untersuchungen von Vitalkapazität und Atemgrenzwert vor und nach dem Gebrauch eines die Bronchien erweiternden Aerosols, wenn es bei beiden zu einem Anstieg kommt. Ein freies Lungenoedem vermindert zuerst die Residualluft und dann die Vitalkapazität. Eine konstriktive mediastinale Pericarditis lässt sich nachweisen durch Herzkatheterisierung als ein Engpass in der Klappenschlusswelle des rechten Ventrikels.

Erkrankungen mit Lungenfibrose können abgegrenzt werden vom Emphysem anhand einer verringerten totalen Lungenkapazität und einem relativ normalen alveolären Stickstoff, begrenzter Vitalkapazität und Residualluft.

Ein verminderter Sauerstoffaustausch in Ruhe und bei Belatung tritt beim Syndrom des alveolo-kapillären Blockes auf, selbst wenn die Haemoglobin-Sättigung normal ist. Sie tritt auch ouf in Fällen, in denen eine geschädigte Durchströmung einer Lunge oder von Teilen einer Lunge vorliegt als Ausdruck einer Gefässverödung oder eines beeinträchtigten Herzminuten-Volumens. Sie bleibt bei Belastung erniedrigt, wenn der Defekt fixiert ist, wie es vorkommt bei Einbeziehung der Arteria pulmonalis in bösartiges Wachstum. Ist das Neoplasma operabel, so beeinflusst es den pulmonalen Blutstrom nicht, und der Sauerstoff-austausch ist in Ruhe normal und steigt unter Belastung an.

Cardiopulmonale Funktionsprüfungen vor und nach Belastung bestimmen die Abgrenzung der thorax-chirurgischen Therapie. Die Angiocardiographie zeigt durchblutungsstörungen in den Lungen an.

Gasanalysen aus der Arteria brachealis zeigen eine Hyperventilation an mit vermindertem CO_2 und Herabgesztem pulmonalen Diffusionsvermögen, sofern der Sauerstoffgehalt niedrig ist (und das Herz normal).

Bei bilateralen Lungencysten zeigt ein niedriger Saurstoffaustausch die Ventilation einer nutzlosen (nicht durchströmten) Lunge an. Bei der Mitralstenose ist der alveoläre Durchmesser verdoppelt infolge eines er-

höhten pulmonalen Capillardruckes, der sich seinerseits in einem erhöhten Residual-Volumen widerspiegelt.

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Epithelium in Tuberculous Pulmonary Lesions*, **

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During the last decade the availability of surgical material has stimulated morphologic observations of tuberculous pulmonary lesions not only for academic purposes, but also with a view to indications for surgery. This has led to divergent interpretations and inconsistent clinical conclusions. Contradictory explanations concerning epithelium, so frequently found in the lesions, have been the main cause of this divergence.

Based upon the material available at Oteen we have attempted to analyze the evidence which has led to such difference in opinion, and have met with facts not previously reported which tend to clarify the picture. This paper deals mainly with the formation and healing of tuberculosis cavities. We are convinced that more consideration must be given to the bronchial tree than before. It appears that some still widely accepted views are no longer tenable.

Pagel and Simmonds[1] believe that in one mechanism of cavity healing ingrowth of epithelium occurs after the tuberculous process has been replaced by ordinary granulation tissue and fibrosis. Auerbach et al[2, 3, 4] support this view, and express the opinion that this type of healing is rare except following streptomycin therapy where it is said to be nearly constant. According to them "re-epithelialization" of the "bronchocavitary junction" occurs regularly in the course of streptomycin therapy and "in some instances the epithelium extends far around the cavity wall," preventing cavity closure. This is contrasted to non-streptomycin treated cases where they report that cavity closure follows bronchial occlusion, but Silverman et al[5] find that this very mechanism of closure follows streptomycin therapy, and do not mention epithelialization.

Both Auerbach and Silverman agree that the cavity contents are potentially dangerous. However they disagree in the reasoning about the danger. Silverman, who claims that early cavity closure occurs with chemotherapy, is fearful about the subsequent retention of infectious material. Auerbach argues that the danger is brought about by non-closure of the cavity because of "re-epithelialization" induced by chemotherapy and is apprehensive about the infectious material because it can not be retained. Both conclusions cannot stand. Both authors have advised resection.

In addition, Silverman, et al suggest the possibility that a cavity may start in a bronchus, but add that by the time the specimen is seen there is too much parenchymal involvement to permit clarification of this point. They also express the belief that tuberculous bronchitis occurs mainly following cavitation since none of their 22 cases had bronchitis

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**Presented as part of an exhibit at the annual meeting, National Tuberculosis Association, Milwaukee, Wisconsin, May 23-27, 1955.

without cavitation.

According to Clegg,[6] ulcero-caseous tuberculous bronchitis, progressing from the periphery to the hilus, is a very important mechanism in the development and spread of the disease. Bronchial stenosis leads to collapse when pneumonia does not occur. Coalescent lesions may produce bronchial cold abscess, either solitary or multiple, which may be evacuated leaving a cavity. He further says that it is often impossible to distinguish in a fully developed caseous lesion whether it arose from tuberculous pneumonia or bronchitis.

Previous authors have tacitly assumed that when epithelium lines structures devoid of muscle, cartilage and glands it is newly formed and hence its presence has been ascribed to epithelialization. It must be borne in mind that while the presence of the epithelium is a fact, the idea of epithelialization is speculative only and implies that the epithelium has not previously existed at the site where it is found. Our study has furnished evidence that epithelium alone identifies bronchial wall with as much certainty as does muscle, cartilage or glands. Our evidence is presented.

If epithelium can be used to identify bronchial wall, what appears to be a parenchymatous cavity lined by epithelium, may be an ectatic bronchus. Figure 1 is a schematic representation of mechanisms which,

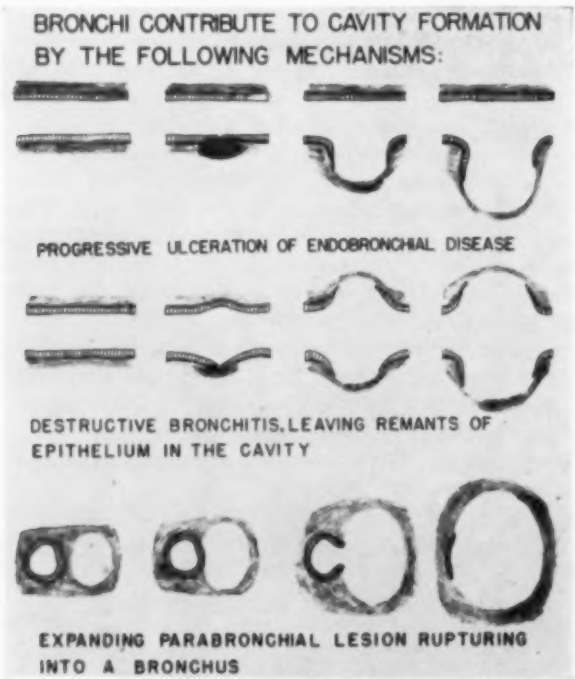

FIGURE 1

according to our experience, produce such epithelialized structures. As a result of destructive endobronchial or parabronchial disease portions of the wall become ulcerated and weakened. Dilatation or distortion follows and irregular epithelial islands may remain. In this way the appearance of a more or less epithelialized cavity is created.

Of the specific bronchial structures, epithelium, glands, muscle and cartilage, epithelium may be the sole survivor because of its resistance to destruction. Even in contact with an acute caseating lesion, bronchial wall, and especially its epithelium, is not easily destroyed (Figs. 2, 3, 4, and 5). When epithelium is destroyed, regeneration depends upon the character of the bed which is to be covered. In *acute* disease such as influenza, regeneration of bronchial epithelium is so active that it may mimic a neoplastic process, as pointed out by Winternitz, et al.[7] Regeneration occurs promptly over a well vascularized surface. However, when *chronic* inflammation has destroyed surface epithelium, re-epithelialization does not seem to occur. In the end stage of open-healed tuberculous cavities treated with or without chemotherapy the wall is composed of dense hyalinized fibrous tissue (Fig. 6A). In addition to such open-healed cavities, this inability to regenerate is observed in other conditions whenever an equally poor "bed" is provided. We have seen this phenomenon in abscess (Fig. 6B) and in infected bronchiectasis (Fig. 6C).

This view is supported by the experiments of Condon,[8] who studied epithelial regeneration of the mucosa of the rat's trachea at various intervals following trauma. He found that the extent of regeneration at any interval was inversely proportional to both the depth of the injury and the amount of inflammatory reaction. These factors determined the

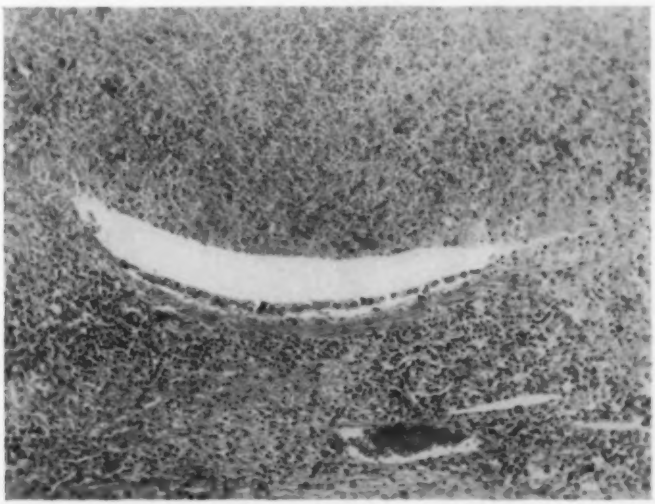

FIGURE 2: Acute expanding lesion in a terminal bronchiole meeting resistant wall. Epithelium and muscle are preserved. 100×.

properties of the surface over which epithelium must grow. The influence of the character of the bed to be epithelialized is thus demonstrated. Condon used healthy animals with small lesions, the epithelium regenerating over an otherwise physiological area. It is hard to conceive that epithelium would grow to line a tuberculous parenchymatous cavity because there the bed is extremely unfavorable. The prolonged and destructive stages of inflammation, caseation and fibrosis, create an almost avascular and impermeable structure, the typical lining of an open-healed tuberculous cavity.

When cartilage, muscle, or glands, singly or in any combination are present, no difficulty of identification of bronchial wall is met. Of these components, muscle is most often found. If a fairly intact segment of bronchial mucosa is seen in the wall of a lesion (Fig. 7), or if any other specific structure such as cartilage is present (Fig. 8), identification is certain. In the presence of epithelium only, it had been postulated by others that (a) the structure covered is not bronchial wall, and that (b) the epithelium is newly formed. No good cause was ever shown for this postulation.

Evidence to distinguish whether an epithelialized structure is bronchial wall or not seems to be missing when bronchial epithelium remains while cartilage, muscle, and glands are not seen. What determines

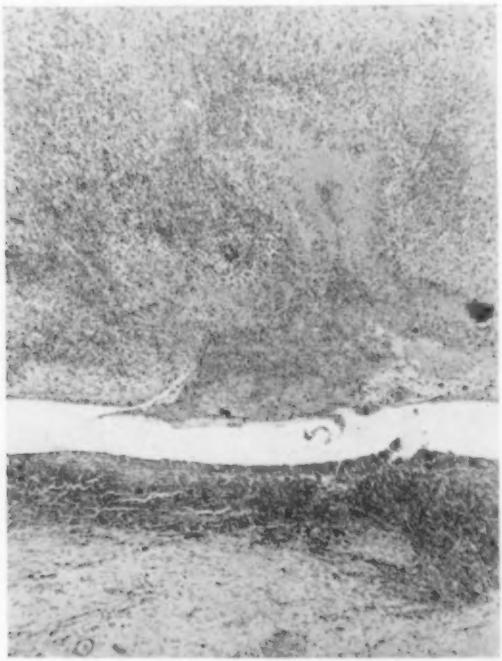

FIGURE 3: Tuberculous bronchitis. One side of the wall is destroyed; the opposite side shows preserved epithelium but no other specific structures. 50×.

whether bronchial wall is present or not in a given structure when only epithelium remains? Our observations have revealed the following:

1. The shape of even non-epithelialized structures may be such that recognition of bronchus is certain (Fig. 9).

2. The epithelialized structures sometimes contain scattered and minute remnants of identifying elements. In Fig. 2 bronchial wall at the edge of a caseating lesion is identified by the muscle. These structures which can be recognized by fragments of such specific elements are

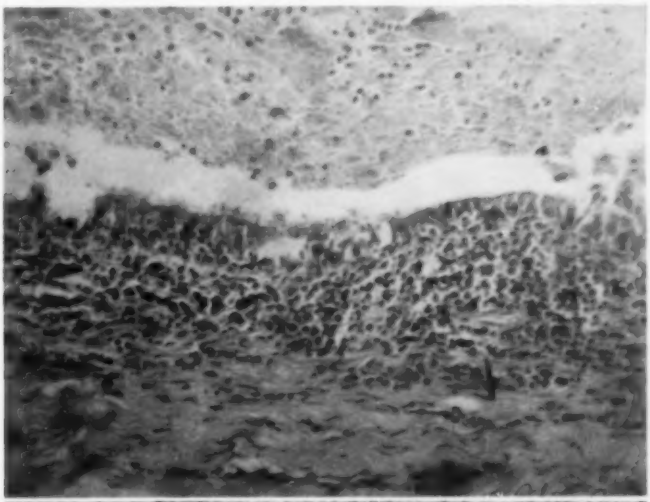

FIGURE 4

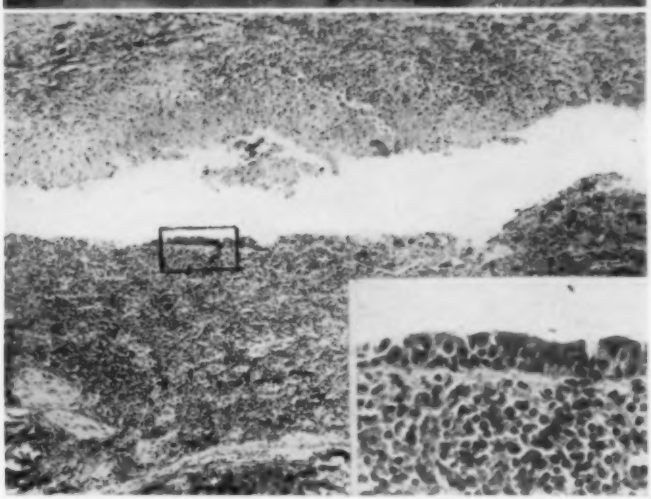

FIGURE 5

FIGURE 4: A segment of columnar ciliated epithelium lines the capsule of a caseous nodule. 140×.—FIGURE 5: Tuberculous bronchitis. Narrowed cavity with remnants of columnar epithelium. Without this epithelium identification is impossible. 60×. Insert 200×.

identical in all respects with those where they are absent (Fig. 3).

Assuming that an epithelialized structure has been identified as bronchial wall by the presence of a muscle fragment, would it not be incongruous to assert that the very same structure is not bronchus because no muscle fragment is seen in a neighboring section?

We believe epithelium to be an identifying element as are the others, and that all epithelium-bearing structures under consideration are bronchial walls. Alternate interpretations would require *ad hoc* postulation and would be more speculative.

The terms "broncho-cavitary junction" and "re-epithelialization," we believe, have been inappropriately used by some. The broncho-cavitary junction can be defined only in a macroscopic sense as the place where a relatively narrow structure joins a wide one. Microscopic examination may reveal that a portion of the wider structure is still bronchial wall which has been ectropionized and dilated (Figs. 1 and 10). The term "re-epithelialization" was misused because the authors meant that epithelium had grown on a newly formed surface. The proper use of this term would infer replacement of pre-existing epithelium.

We do not believe that epithelium ever forms the lining of a parenchymatous cavity; that any epithelium found in an open cavity is best interpreted as an indication of underlying bronchial wall.

It may be interesting to note that more and more non-epithelialized cavities have been observed since the advent of chemotherapy, though they have been seen without chemotherapy. In the last stage of healing, giant cells are consistently present as a lining of the hyalinized fibrous tissue wall. They sometimes resemble epithelium (Fig. 6D).

FIGURE 6A FIGURE 6B FIGURE 6C FIGURE 6D

FIGURE 6: 125×. A. End stage of healing of a tuberculous cavity without chemotherapy. B. Healed post-abscess cavity wall, non-tuberculous. C. Healed Bronchiectatic "cavity" without "re-epithelialization." D. Tuberculous cavity. Nearly healed portion lined by giant cells. The structure is similar in all cases.

Conclusions

1. Bronchi participate extensively in tuberculous cavity formation.

2. The presence of epithelium in the lining of a "cavity" identifies bronchial wall.

3. Open-healing of tuberculous parenchymatous cavities does not lead to epithelialization.

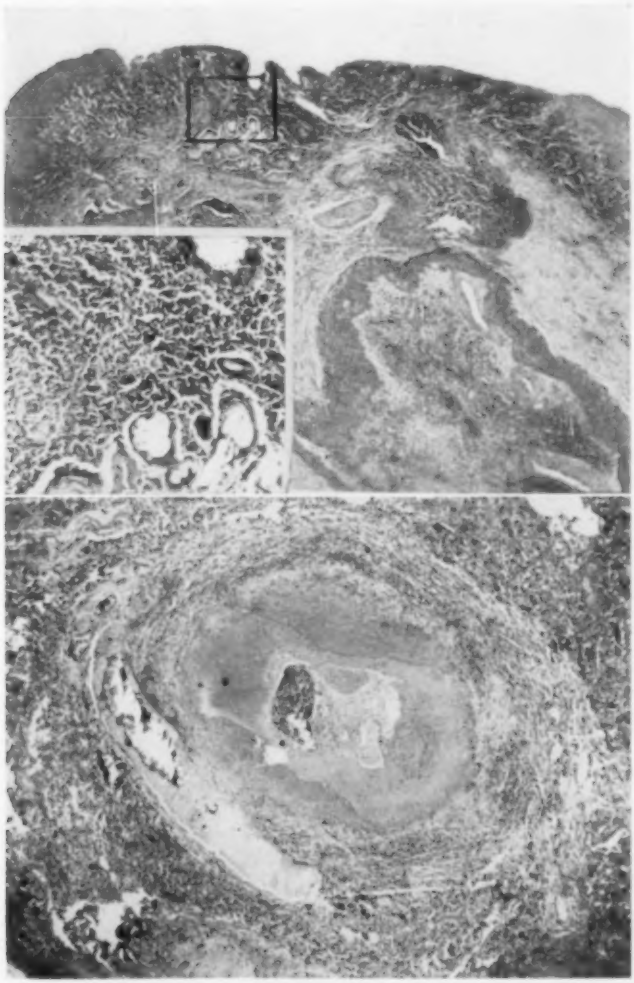

FIGURE 7

FIGURE 8

FIGURE 7: A bronchial segment forms part of a tuberculous cavity wall. Mucous glands and columnar epithelium are preserved. 20×. Insert 200×. FIGURE 8: A caseous lesion originating from bronchitis. Without the chance finding of cartilage and desquamated epithelium, this lesion would be confused with a parenchymatous nodule. 40×.

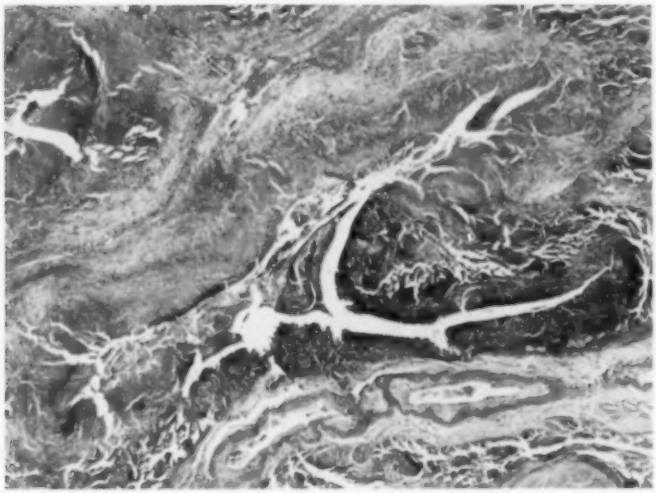

FIGURE 9: Y-shaped bronchial structure. The preserved limb permits identification. 10×.

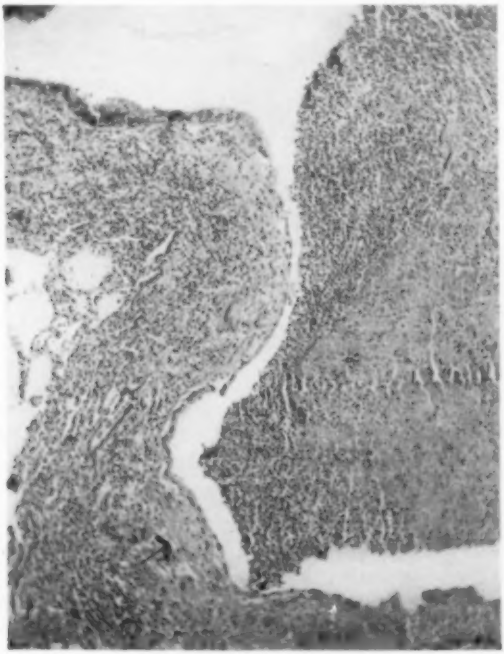

FIGURE 10: "Broncho-cavitary junction." No chemotherapy. Muscle (arrow) identifies bronchial wall. In the absence of this or other identifying elements this frequently seen picture (note mechanisms, Figure 1) has been erroneously interpreted as "re-epithelialization" of the "broncho-cavitary junction." 75×.

SUMMARY

Epithelium found in the lining of tuberculous cavities has been generally interpreted as the result of epithelialization. Our evidence supports the concept that such epithelium is instead a remnant of bronchial wall.

Open-healed cavities are devoid of epithelium and remain so because the infection produces dense fibrous tissue which is permanently incapable of supporting epithelial growth. Similar situations prevail in non-tuberculous cavities (post-abscess and suppurative bronchiectasis). It is concluded that epithelium found on what appears to be cavity wall is not newly formed but identifies bronchial wall.

RESUMEN

El epitelio encontrado en la superficie de las cavernas tuberculosas se ha considerado generalmente como un resultado de la epitelización. Nuestras evidencias apoyan el concepto de que tal epitelio es un resto de la pared bronquial.

Las cavernas abiertas curadas carecen de epitelio y así permanecen porque la infección produce tejido fibroso denso que es permanentemente incapaz de soportar el crecimiento del epitelio. Situaciones semejantes se encuentran en las cavidades no tuberculosas (post-abscedales y bronquiectasias supurantes).

Se concluye que el epitelio encontrado en lo que parece ser la pared de la caverna no es nuevo, sino que se identificó la pared bronquial.

ZUSAMMENFASSUNG

Die Anwesenheit von epithelialer Auskleidung tuberkulöser Cavernen ist im Allgemeinen als das Resultat einer neuen Epithelialisierung gedeuted worden. Unser Befunde stützen aber die Auffassung, dass solches Epithel ein Überbleibsel von Bronchialwand ist.

Offen geheilte Cavernen bleiben dauernd von Epithel entblösst, da durch die Infektion ein fibröses Bett geschaffen wird, auf dem kein Epithel mehr wachsen kann. Ähnliche Umstände bestehen in nicht tuberkulösen Cavernen (nach Abszess, eitriger Bronchiektasie). Es wird gefolgert, dass Befunde von Epithel in Cavernen als Anwesenheit von Bronchialwand zu deuten sind.

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The Role of Bronchoscopic Studies in Pulmonary Tuberculosis*

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Much progress has been made in the examination and treatment of bronchial changes due to pulmonary tuberculosis in the last 20 years. Improved instrumentarium, especially in the form of bronchotelescopes, has made the visualization of the whole bronchial tree much simpler and the procedure less trying to the patient. It is possible for the bronchologist to do precise work and observe the changes down to the segmental level, or even describe the subdivision of segmental bronchi in some cases.

Many earlier investigators have aimed chiefly at discovering specific tuberculous changes in the bronchial mucous membrane. Their findings differ considerably, depending upon the type of the material and even more upon the criteria selected for the diagnosis of endobronchial tuberculosis. There have been reports in which all inflammatory changes have been labeled tuberculous. At present, however, it is agreed in most centers that such changes as may equally well be due to any other irritation or nonspecific infection, viz. redness, hyperemia and edema of the mucous membranes, are not accepted as specific.

Granulations and ulcerations in the mucous membranes, fibrostenosis and fistulae in tuberculous patients may be considered specific changes due to tuberculous bronchitis. With these criteria earlier workers [3, 7-11] have reported frequency figures generally not exceeding 20 per cent. The figures differ somewhat ranging from McNab's 13 per cent to Jarman's 25 per cent.

In autopsy material the percentage of tuberculous bronchitis is generally much greater. It is obvious, however, that in a non-resistant body terminal lesions increase out of proportion and therefore autopsy figures cannot be correlated with clinical findings. Only the material obtained at pulmonary resections is comparable to bronchoscopic observations. Yet it must be remembered that the bronchotelescopes do not permit visualization of the medium sized and small bronchi, where tuberculous bronchitis can be demonstrated in pathological specimens.

Indeed, it was observed by Meissner[12] and by Buckles and Neptune[1] that tuberculous bronchial lesions increase towards the periphery and that there is often a continuity from the parenchymal process to the supplying division of the segmental bronchus. Taking all these lesions into account, specific microscopic changes were observed in over 50 per cent. Although resected material is highly selected, consisting of cases with far advanced segmental or lobar changes, it is evident that tuberculous alterations are likely to increase as the bronchial lumen decreases in size.

Having this in mind, it seems to us that in the examination of patients

From the Satakunta Sanatorium.

*Presented at the Fourth International Congress on Diseases of the Chest, Cologne, Germany, August 19-23, 1956.

suffering from pulmonary tuberculosis, a segmental bronchoscopy—however skilfully performed — does not mark the end of the bronchoscopist's responsibility. More information is needed especially of the condition of the medium sized and smaller bronchi by means of a bronchogram, and of the activity of the disease by cytologic and bacterial studies of the bronchial aspirate.

Observations

The observation period in this series of over 500 bronchoscopies extends from October 1954 to May 1956. We do bronchoscopies routinely for each case before any collapse or operative procedure and about one half of the whole material is included in this indication category. Bronchial evaluation of the activity of the disease and differential diagnosis form the second largest indication groups. Other indications, like hemoptysis or atelectasis, are partly included in the former groups, but as sole indications they form only a small minority. The large size of the surgical indications group is due also to the fact that these cases need early decision. Therefore, they are given preference over patients with other indications.

About half the series consists of cases of moderately advanced tuberculosis. Nearly one third are classified as far advanced and the rest form a group with minimal changes. The number of patients in each of these three clinical groups agrees closely with the corresponding groups in Finnish sanatoria in general.

During their present stay in the sanatorium most patients had received medication before bronchoscopy. Only 5 per cent had had no antibacterial treatment of any kind. Streptomycin, PAS and INH had been given in most instances. Sometimes penicillin or oxytetracycline had been administered in evident mixed infections.

Anesthesia was induced after the usual barbiturate, atropin, morphium premedication with ½ and presently with ¼ per cent pontocain in which 8 drops 1:1000 adrenalin and 200 units of "Luronase" for each 40 cc. of the solution was added. It seems that the use of hyaluronidase in the form of "Luronase" clearly added to the anesthetic power: we obtained satisfactory anesthesia with generally less than 10 cc. of ¼-½ per cent pontocain. Apparently the use of fractionated weak solutions is also the reason why there occurred no single toxic reaction due to the anesthetic.

Bronchoscopic observations: In these 500 cases we found changes indicating bronchial tuberculosis in about 10 per cent. The criteria consisted in the alterations mentioned earlier as signs indicating bronchial tuberculosis. Hyperemia and edema were also noted but only as nonspecific changes. Whenever possible, the diagnosis of tuberculous bronchitis was confirmed by a biopsy specimen. The result of microscopic examination was almost always consistent with the clinical judgment. On the other hand, in the case of 19 biopsies taken from cases with various degrees of hyperemia and slight edema the microscopic specimen showed no tuberculous change.

Biopsy is still often viewed with doubt in tuberculous cases because it is feared that a permanent ulceration will develop at its site. We repeated bronchoscopy in many of these cases after an interval of a few weeks, but there was no sign of any irritation due to the biopsy.

It was noteworthy that there was no clear macroscopic tuberculous ulceration of the mucous membranes. Endobronchial tuberculosis manifested itself in the form of granulating surfaces, often associated with severe bronchitic changes. It seems obvious that the use of antituberculous medication is responsible for this changing pathology.

In many cases there were clear segmental alterations. Some were old, inactive relative stenoses of the segmental orifices, some were active changes. An irritated segmental orifice, possibly with slight or severe inflammatory stenosis and purulent secretion, clearly pointed the way to an infected segment with an active process. It also offered a good opportunity to remove secretions for cytologic and bacterial studies.

Bronchographic observations: An evaluation of the first 99[13] cases in our series showed that the bronchial alterations were obviously in some instances far more severe than our bronchoscopic records indicated. These changes were beyond the limits of the telescopes and could be definitely demonstrated only with a bronchogram. For the following series of 102[4] cases we made a bronchogram for about one fourth of the cases. As the results proved valuable and there was no untoward effect, we now supplement each bronchoscopy with bronchography on the affected or worse side.

We found the oily "Lipiodol" solution best suited for successful bronchography. To each 20 cc. ampoul is added 6 gm. fine sulphatiazol powder[2]

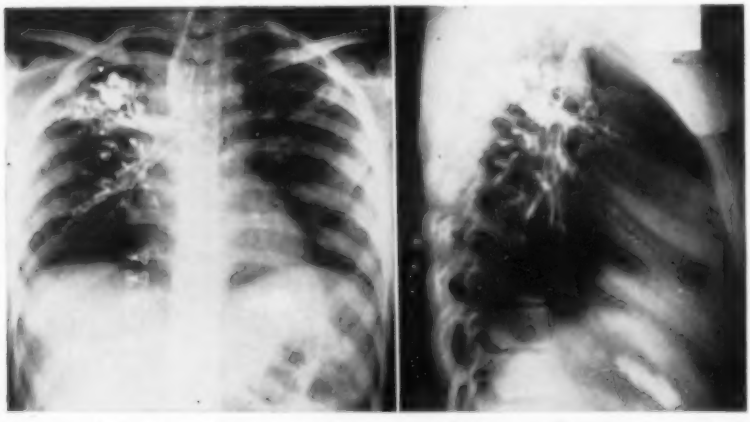

FIGURE 1: Case 346, a farmer's daughter, aged 22 years. The process in the lungs had begun in 1953 but bacilli were not found till 1955. In 1953 INH and PAS were given; during the present stay she received streptomycin, PAS and INH. In the tomographic films small clear areas were seen in the right upper lobe but no cavitation was observed on either side. Thoracoplasty was contemplated on the right side. Bronchoscopy revealed a moderate amount of secretion in the left main and lower lobe bronchi, but otherwise the bronchial tree was normal. In the right side the upper lobe segmental branches were without pathology; in the middle and lower lobe bronchi there was much secretion and slight bronchitis. The bronchograms demonstrated large saccular bronchiectasis in the right posterior and apical segmental bronchi. Due to secretion, the filling of the middle and lower lobe peripheral bronchi is incomplete. The aspirates presented numerous leukocytes on the right side. Cell clusters were observed on both sides. Bacterial culture showed Neisseriae (crassa and flava) and streptococci (salivarius and mitis). Fungi were not found.

and the mixture is warmed to body temperature. 10-12 cc. of this mixture is syringed via a rubber catheter through the bronchoscope which is thereafter gently withdrawn. The addition of powdered sulfa seems almost always to prevent the oil entering the alveoli. Nevertheless the bronchial tree fills well with oil which is expectorated after a few hours. It may also be that the antibacterial properties of lipiodol-sulfa mixture can be beneficial especially in cases with large bronchiectatic cavities.

When bronchography is made routinely in combination with bronchoscopy, it is surprising to notice how often there is marked pathology in the medium sized and smaller bronchi. Cylindrical bronchiectasis can be found in almost all phases of the disease and they increase in number as the disease becomes worse and more chronic. Saccular bronchiectasis seems to belong to the far advanced stage and can be seen especially in cases in which thoracoplasty has been performed without the disease being arrested.

It seems to us that if enough bronchograms are made, ideal cases for thoracoplasty will decrease considerably in number, and resection must be increasingly employed. It may be that sometimes the ectatic bronchi are involved by the specific disease, while sometimes the changes are nonspecific. Especially in the former case the process may be persistent in spite of a successful collapse.

Cytologic studies: We have stated earlier[13] that it is seldom possible to use bronchial aspirates as diagnostic means in pulmonary tuberculosis. In our experience the presence of Langhans giant cells is so rare that it has no practical importance. Epithelial cell clusters which have been suggested as diagnostic criteria[5] seem to occur also in nontuberculous diseases. Nevertheless their presence in large numbers indicates an active process in the mucous membranes where the cells break off in large numbers, often down to the basal cell layer or even to the basal membrane.

The presence of polymorphonuclear leukocytes in large numbers seems to

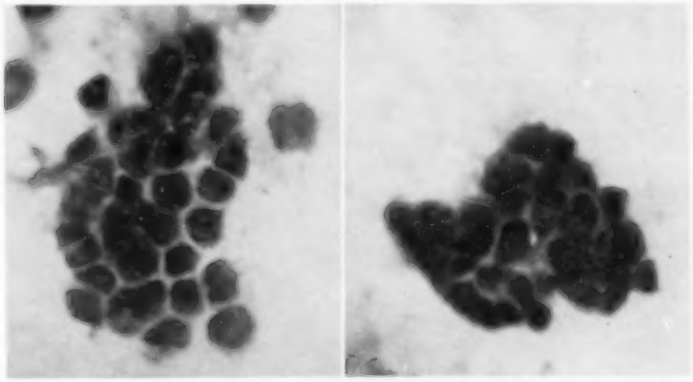

FIGURE 2: Two epithelial cell clusters show cells arranged in tissue-like fashion with clear nuclei but only a rim of cytoplasm in most cells. The group on the left side is derived from a case showing tuberculous endobronchitis, the group on the right from a case with normal bronchial mucous membranes.

occur in our material especially in cases of tuberculous bronchitis, bronchiectasis, or severe nonspecific bronchitis. Although it is not possible to say which of these conditions may be responsible for their presence, this finding indicates an active process and needs special attention.

Bacteriological studies: Tubercle bacilli were sought in every aspirate by means of staining and culture. They were demonstrated in 20 per cent of the material. This rather low figure probably also indicates the effect of antituberculous medication. As would be expected the incidence of bacilli increased with the severity of the clinical alterations.

Non-specific organisms were sought in 133 aspirates.[4] The number of pathogenic bacteria was not large, but it was observed that in general the number of bacteria agreed closely with the bronchitic changes. Gram negative rods, which did not grow in cultures, were seen almost exclusively in the smears of bronchitic cases. This finding, and the large-scale bacterial phagocytosis by alveolar phagocytes, indicates an invasion of the lower airways by the upper respiratory flora in cases with lowered resistance of the mucous membrane.

It is obviously not feasible to make a full bacterial analysis of every case subjected to bronchoscopy. We found it to be a good practicce in all cases scheduled for a major operation in the near future, and in cases not yet definitely diagnosed. In these two groups additional information may be helpful with a view to the proper treatment of the patients.

SUMMARY

Experiences based on over 500 bronchoscopies at Satakunta Sanatorium are reported. It is emphasized that bronchoscopy alone is not sufficient for a complete bronchial evaluation because its field is limited to the main and lobar bronchi and segmental orifices.

Bronchography gives invaluable information of the condition of medium sized and small bronchi. It is performed via the bronchoscope with a lipiodol-sulpha mixture which as a rule does not enter the alveoli. Bronchoscopy reveals endobronchial tuberculosis in about 10 per cent of the cases, but the number of pathological bronchi increases to nearly 50 per cent when the information of the bronchograms is added.

Cytologic studies are used to indicate the severity of infection and to reveal the condition of the ciliated epithelium by examining the aspirates for polymorphonuclear leukocytes and exfoliated groups of surface epithelium.

Bacterial studies are of importance especially before any major operations and in all undiagnosed cases.

RESUMEN

La experiencia basada en más de 500 broncoscopías en el Sanatorio Satakunta son relatadas. Se recalca que la broncoscopía sola no es suficiente para una valoración completa del estado de los bronquios porque su campo es limitado a los bronquios principales y a los orificios segmentarios.

La broncografía da invaluable información sobre las condiciones de los bronquios medianos y pequeños. Se hace a través del broncoscopio usando la combinación lipiodol-sulfa que como regla, no entra en los alveolas.

La broncoscopía revela la tuberculosis endobronquial en cerca de 10 por ciento de los casos, pero el número de bronquios patológicos aumenta hasta 50 por ciento cuando la información del broncograma se agrega.

Los estudios citológicos indican la severidad de la infección y revela el estado del epiteliociliado por el examen de los productos de aspiración en busca de leucocitos polimorfonucleares y los grupos de células exfoliadas del epitelio superficial.

Los estudios bacteriológicos son de importancia especialmente antes de operaciones mayores y en casos dudosos.

ZUSAMMENFASSUNG

Es werden die Erfahrungen mitgeteilt, die sich aus mehr als 500 Bronchoskopien in Satacunta-Sanatorium ergaben. Es wird hervorgehoben, dass die Bronchoskopie allein nicht ausreicht zur vollstädigen bronchialen Untersuchung, da ihre Möglichkeiten beschränkt sind auf die Haupt- und Lappen-Bronchien und die Eingänge der Segmentbronchien.

Die Bronchographie liefert unschätzbare Informationen über den Zustand der mittelgrossen und kleinen Bronchien. Sie wird ausgeführt auf bronchoskopischem Wege mit einem Lipjodol-Sulfa-Gemisch, das im Regelfall nicht in die Alveolen eindringt. Die Bronchoskopie ergibt eine Endobronchiale Tuberkulose in etwa 10% der Fälle, jedoch steigt der Zahl der pathologisch veränderten Bronchien auf ungefähr 50, wenn die Information der Bronchogramme hinzukommt.

Zytologische Untersuchungen werden angestellt, um hinzuweisen auf die Schwere der Infektion und die Beschaffenheit des Flimmerepithels aufzudecken mittels Prüfung der angesaugten Flüssigkeit auf gelapptkernige Leukozyten und abgestossene Zellgruppen des Oberflächenepithels.

Bakteriologische Untersuchungen sind von Bedeutung, besonders vor allen grossen Operationen und in allen fraglichen Fällen.

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The Changing Picture of Lung Abscess Therapy

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The prognosis and management of lung abscess has changed dramatically within the past 15 years. The purpose of this paper is to illustrate this by reporting our experience with 65 patients seen and treated since 1941.* Not only has the mortality been remarkably lowered but the morbidity, as measured by duration of hospitalization, has improved. The paper will report our experience with the use of Tryptar as an adjunct in the therapy of this problem, which we believe has been of considerable value.

Material and Methods of Treatment: Medical measures were applied in all cases and surgery instituted as indicated. The 65 cases in Table I divide themselves readily in three groups, Group A, 1941-44, 19 cases; Group B, 1945-51, 29 cases; Group C, 1952-55, 17 cases.

TABLE I
LUNG ABSCESS GROUPS

	A	B	C	TOTAL
Groups	1941-1944	1945-1951	1953-1955	1941-1955
Cases	19	29	17	65

Group A—1941 to 1944: The sulfonamide period; treatment consisted of supportive measures, bronchoscopic aspirations, postural drainage, sulfonamides and surgical procedures. Bronchoscopy was used routinely in all cases, both as a diagnostic tool and also as a means of cleansing the tracheal bronchial tree. Sulfonamides were used in various dosage regimens and the drugs were Sulfathiazole and Sulfadiazine. Surgical procedures were simple incision and drainage or two-stage pneumonotomies.

Group B—1945 to 1951: The penicillin period; this drug was used both parenterally and by the aerosol route. Supportive treatment was unchanged, postural drainage was enforced, bronchoscopy was used as a diagnostic and therapeutic agent. Surgical procedures were the same as Period A, except that from 1949 on resection was carried out in the majority of cases requiring surgical intervention.

Group C—1952 to 1955: The antibiotic and tryptar period; supportive treatment remained unchanged. Bronchoscopy was used routinely but

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are their own and do not reflect the opinion or policy of the Veterans Administration. From Veterans Administration Hospitals, Augusta, Georgia and Oteen, North Carolina.

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only as a diagnostic aid and a means of securing accurate cultural material. The antibiotics used were Terramycin, mainly, and Penicillin and Achromycin to a lesser extent. The drug used was selected from sensitivity studies of material obtained at bronchoscopy, prior to instituting therapy. Aerosol administration of the most efficacious drug was used in all cases. In about one-half of the cases, oral or parenteral administration of antibiotics was used also, especially for the first few days after admission. Tryptar* by aerosol administration was used in all this group. This was administered 125 gms. in 2 cc. of diluent daily for five to 10 days, and then every second day for a period of from two to four weeks. Surgery, during this Period C, was in each case resectional. No surgical drainage procedures were done.

Pathogenesis and Etiology: It is our belief that bronchial or bronchiolar obstruction by any one of several causes, foreign bodies, inflammation, or aspirated secretions, leads to an area of atelectasis which, when followed by infection, leads to vessel thrombosis and this to an area of infarction. Infection plus infarction leads to tissue necrosis and suppuration.[1, 2, 3, 4]

The precipitating cause of lung abscess falls into one of five broad groups: (1) Unconsciousness from any cause, trauma, anesthesia, epilepsy, drug narcosis, insulin shock, diabetic coma, alcoholic intoxication; (2) Acute infections, pneumonia of pyogenic or viral origin, and severe upper respiratory tract infections; (3) Foreign body aspirations, teeth, tonsillar tissue, peanut shells, beans, etc.; (4) Penetrating wounds of the lung resulting from fractured ribs, ice pick or knife injuries, gunshot wounds or other penetrating foreign missiles; (5) Idiopathic, in this large group are those cases in which no amount of investigation yields a clear-cut cause. The etiologic agents in this series (Table II) show the three groups to be roughly comparable. The most frequent cause remains acute pulmonary in-

TABLE II
PREDISPOSING FACTORS

GROUPS	A	B	C
1. Unconsciousness			
(a) Anesthesia	3	1	2
(b) Alcohol			2
(c) Convulsion			1
2. Pulmonary Infarction			
(a) Pneumonia	4	8	2
(b) Upper Respiratory Infections	5	4	3
(c) Influenza		1	2
3. Foreign Body		1	
4. Injuries, Penetrating			
(a) Fractured Ribs		2	
5. Idiopathic	7	12	5

*Tryptar, Armour Brand Lyophilized Chrystaline Trypsin.

fections, although lobar pneumonia has decreased in the most recent period (Group C). Alcoholic excess appears as a cause in a surprisingly small number of cases. This we regard as fallacious and it was our impression that alcoholic excess was a frequent factor in many of our cases.

Bacteriology: The bacteriology of these lung abscesses was somewhat surprising inasmuch as in all groups it was usual to find only Streptococcus viridens, Staphylococcus albus, or Micrococcus catarrhalis (Table III). Pathogenic bacteria were rather infrequently found. Drake[5] recorded a similar experience. One may attribute this finding to the patients having been treated with antibiotics, briefly, on the outside prior to hospitalization. Inasmuch as this trend extended back prior to the sulfa period, one wonders if the infecting organism is not of secondary importance and the local factors, i.e., obstruction, atelectasis, thrombosis, of far greater import. In our series at least, putrid versus non-putrid lung abscess has not, it seems to us, been worthy of differentiation. Most patients note a foul sputum for a day or so at the beginning of evacuation of the abscess, but, once it begins to empty well, the sputa, while still purulent, becomes no longer putrid. This may be attributed to the use of drugs and to the fact that once the abscess begins to evacuate there are no longer optimum anerobic conditions present necessary for the growth of the fusiform bacilli and spirochetal organisms which cause the putrid odor.

Results: The mortality and morbidity in this series is shown in Table IV. One notes that there has been a satisfying fall in mortality in these 14 years. The figure of 31.5 per cent in the period 1941-1944 (Group A) reflects the general mortality figures at that time. With the advent of penicillin, 1945-1952 (Group B), there was for the first time a significant drop in mortality to 17.2 per cent for this group. The present group,

TABLE III
BACTERIOLOGY

GROUPS	A	B	C
Organism			
Alpha streptococci	3	8	12
Staph. albus	5	3	1
Diplococcus pneumoniae	3	3	1
Beta streptococci	1	3	2
Staph. aureus	2	3	1
Enterococci		3	1
M. catarrhalis	1	2	1
Candida albicans		1	2
Klebsiella pneumoniae		1	2
H. influenzae		1	
Serratia			1
Herrellea			1

TABLE IV
MORTALITY (MEDICAL, SURGICAL, COMBINED)

GROUPS	A	B	C
Medical			
Well	6	11	11
Died	1	0	0
Per Cent	16.6	0.0	0.0
Surgical			
Well	13	18	6
Died	5	5	0
Per Cent	38.5	27.7	0.0
Combined			
Well	19	29	17
Died	6	5	0
Per Cent	31.5	17.2	0.0

1952-1955 (Group C), with no deaths, has been a gratifying experience.

Not only has mortality been reduced with each group, but morbidity as measured by duration of hospital treatment has likewise improved (see Table V). The average period of 6.6 months in Group A, compared with 4.2 months in Group B, and 3.2 months in Group C, is ample proof.

Discussion: Several factors have contributed to the improvement in the treatment of lung abscesses in the past 14 years. Of perhaps greatest importance has been the availability of effective antibiotics. The preferable route of administration of the antibiotic has been debated. All cases in Group C, and to a large extent Group B, received antibiotics by the aerosol route. That good therapeutic levels may be obtained by this means has been adequately shown.[6, 7] Gaensler[8] produced evidence that the aerosol route of administration may be even more effective than the parenteral or oral route. We feel that both aerosol and oral or parenteral therapy combined is the best. Oxytetracycline* was the drug most frequently used because of the availability of an aerosol preparation and because organisms isolated were usually sensitive to this drug.

The early diagnosis and treatment of lung abscess has probably been of considerable import in the reduction of mortality and morbidity. In all groups, there has been a steady fall in the duration of symptoms prior to admission and beginning of treatment (Table VI). In Group A the average was 6.9 months, in Group B the average was 5.3 months, and in Group C the average was 3.6 months. It is worth while to point out the

TABLE V
MORBIDITY (MONTHS IN HOSPITAL)

GROUPS	A	B	C
Average Months Hospitalized	6.5	4.2	3.2

*Rx: Terramycin, Pfizer.

TABLE VI
DURATION SYMPTOMS PRIOR TO HOSPITALIZATION
(AVERAGE NUMBER OF MONTHS)

GROUPS	A	B	C
Medical	4.8 mo.	2.9 mo.	1.8 mo.
Surgical	8.9 mo.	7.6 mo.	5.1 mo.
Combined	6.9 mo.	5.3 mo.	3.6 mo.

consistent difference between those cases cured medically and those requiring surgery. It has been consistently found, in all groups, those cases with the shortest antecedent history prior to admission are those who are most frequently handled without surgery. Group A: Medical 4.8 mos., Surgical 8.9 mos.; Group B: Medical 2.9 mos., Surgical 7.6 mos.; Group C: Medical 1.8 mos., Surgical 5.1 mos.

Whether resectional therapy in place of drainage procedures has helped to improve the mortality rate is open to some question. Table VII shows the difference in mortality, in all groups, between those cases treated surgically by drainage procedures and those resected. This impressive difference, 38 per cent for drainage and 6.3 per cent for resection cases, is misleading since resection would have often been impossible, even today, if the infection had not been controlled by use of effective antibiotics, and possibly also by the addition of Tryptar.

In 1952, it occurred to us that the enzymatic debridement with Tryptar might aid in the therapy of lung abscesses. It was thought that, if adequate drainage of the abscess might be affected early, and well, healing of the lesion might be facilitated. To date, 17 cases have been treated and followed from one to four years. There has been no death in this series and the cure rate without surgical intervention has been high (Table VIII). Approximately 64.7 per cent were medically cured in Group C, as compared with approximately 37.9 per cent in the immediately preceding Group B treated with penicillin, and 26.3 per cent in Group A, the sulfonamide treated series. Limber, et al,[9] report first in 1954 the preliminary studies on the use of Tryptar as a lytic agent in pulmonary diseases. They showed it to be a relatively non-toxic, non-irritating and effective agent in cleansing the bronchial tree. Later, 1954,[10] they reported their clinical experience with Tryptar in a wide range of pulmonary diseases. In their series there were six cases of chronic lung abscesses treated with healing of the abscess in all cases. It has been our impression that our patients become rapidly less toxic with the use of Tryptar and that their secretions were thinned and rapidly decreased in a matter of a few days. The

TABLE VII
SURGICAL MORTALITY (DRAINAGE VS. RESECTION)

	Surgical Cases	Lived	Died	Per Cent
Drainage	21	13	8	38.0
Resection	16	15	1	6.3

TABLE VIII
COMPARISON OF MEDICAL VS. SURGICAL CURED

GROUPS	A Per Cent	B Per Cent	C Per Cent
Medical Cure	26.3	37.9	64.7
Requiring Surgery for Cure	42.1	44.9	35.3
Mortality	31.6	17.2	0.0
TOTAL	100	100	100

high cure rate of course cannot be attributed to Tryptar alone. No toxic reactions have been observed, except for slight soreness of the mouth, which can be readily prevented by having the patient cleanse his mouth thoroughly with water immediately following the aerosol administration.

The indication for resection in all of these cases has been a residual cavity, be it thin-walled or surrounded by dense fibrous tissue membrane. This is in agreement with the feeling of others.[11, 12, 13] Failure to show progressive closures over successive two-week periods is, in general, our criteria for maximal improvement and indicates need for surgical resection. Indications for resection therapy, other than the above, are: associated or residual bronchiectasis and, suspected bronchogenic carcinoma as an etiologic agent. Rappaport[11] has recently emphasized the problem of the thin-walled residual space, or, as he calls it, "The Vanishing Lung." This situation is being seen in increasing numbers since the advent of antibiotics. He feels that these cases should be resected because of their tendency to recur and/or go on to progressive bullae with its damage to normal lung tissues. Two cases in Group C, who had recurrence of their lung abscess 10 and 11 years respectively, after their first occurrence, support this concept.

This problem of the clean-wall residual space has appeared more frequently in the case of tuberculous cavities, especially those treated with Isoniazid. We have resected a number of these cases and have been surprised to find how benign the lesion was. Culturally, these clean-walled spaces have been negative for acid-fast bacilli and it raises some question as to the necessity for resection. It may be pointed out that only in the last few years has the therapy of lung abscess been so effective with the present use of antibiotics, and, in our particular series, Tryptar. There is some reason to wonder whether small residual clean-wall spaces remaining after prolonged chemotherapy and Tryptar debridement may not be left safely. We do not know the answer to this and, at the present time, we are following two patients who have such a situation and who have now been followed from 18 and 24 months with no difficulty to date and with disappearance of their thin-walled space.

In none of our cases in Group C has a drainage procedure been deemed necessary or advisable. Waterman,[1] in a recent excellent paper, lists indications at the present time for drainage procedures as being fulminating cases, poor risk patients, and in simple uncomplicated acute abscesses in

which good results may be expected. We feel that with our present regimen of careful bacteriological studies, postural drainage, selected antibiotics and enzymatic aerosol debridement, nearly all lung abscesses may be either cured or brought to optimal condition for resectional therapy.

ADDENDUM:

Five additional cases have been treated since this report. All have been cured by the regimen used in Group C. None has required resection.

SUMMARY

Sixty-five cases of lung abscesses are reported. These are divided in three groups. The sulfonamide period 1941-1944, 19 cases; the penicillin period 1944-1952, 29 cases; the antibiotic, or tryptar period 1952-1956, 17 cases. Mortality has fallen progressively from 31.5 per cent in the first, to 17.2 per cent in the second, to zero in the latest group.

It is felt that several factors have contributed to the lowered mortality. Treatment has been instituted earlier in each group, a larger number of effective antibiotics have been available, chemical debridement with Tryptar has proved very useful.

Resection has replaced drainage procedures when surgery is needed. Surgical management has been increasingly less necessary in each group, so that in the most recent series 65 per cent required no surgery for cure.

RESUMEN

Se reportant sesenta y cinco casos de abscesos pulmonares. Se les divide en tres grupos. El período de sulfonamida 1941-1944, 19 casos; el período de la penicilina 1944-1952, 29 casos: el período de antibióticos o tryptar 1952-1956, 17 casos. La mortalidad ha decrecido progresivamente de 31.5% en el primero, a 17.2% en el segundo y a cero en el último.

Se percibe que varios factores han contribuído al descenso de mortalidad. El tratamiento se ha instituído más temprano en cada grupo, un número más grande de antibióticos efectivos se hallan disponibles, la debridación química por medio de tryptar ha resultado muy útil.

La resección ha reemplazado a los procedimientos de drenaje cuando se hace necesaria la cirugía. El tratamiento quirúrgico se ha ido haciendo menos necesario cada vez, de tal manera que en las series más recientes el 65% no requirió cirugía para su curación.

RESUME

Les auteurs rapportent 65 cas d'abcès pulmonaires. Ils les ont divisés en trois groupes. Pendant la période des sulfamides de 1941-44, 19 cas furent traités. Pendant la période de la pénicilline, 1944-52, 29 cas furent traités, et pendant la période des antibiotiques ou du "tryptar," de 1953-56, 17 cas. La mortalité est tombée progressivement de 31,5% dans le premier groupe, à 17,2% dans le second, et elle est nulle dans le dernier.

Les auteurs pensent que plusieurs facteurs ont contribué à abaisser la mortalité. Le traitement a été institué plus précocément dans chaque groupe, un plus grand nombre d'antibiotiques efficaces ont été disponibles, et le détergement chimique avec le "tryptar" s'est montré très utile.

La résection a remplacé les procédés de drainage quand il est nécessaire d'envisager la chirurgie. Le recours à la chirurgie a été de moins en moins nécessaire dans chaque groupe, de telle sorte que dans le groupe le plus récent, 65% des malades n'ont pas eu besoin de la chirurgie pour guérir.

ZUSAMMENFASSUNG

65 Fälle von Lungenabszess werden vorgestellt. Diese werden in 3 Gruppen aufgeteilt. Die Sulfonamid-Periode von 1941-1944—19 Fälle; die Penizillin-Periode von 1944-1952—29 Fälle; die antibiotische oder Tryptar-Periode von 1952-1956—17 Fälle. Die Mortalität fiel progressiv von 31,5% in der ersten auf 17,2% in der zweiten bis zu Null in der letzten Gruppe.

Es besteht die Auffassung, dass verschiedene Faktoren zu der herabgesetzten Mortalität beigetragen haben. Die Behandlung setzte mit jeder Gruppe früher ein, eine grössere Gruppe wirksamer antibiotizis stand zur Verfügung, die chemische Reinigung mit Tryptar hat sich als sehr nützlich erwiesen.

War eine Operation notwendig, so hat die Resektion die Methode der Drainage ersetzt. Chirurgisches Vorgehen wurde zunehmend weniger notwendig in jeder Gruppe, sodasss in der jüngsten Serie 65% keinen Eingriff zur Heilung benötigten.

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The Treatment of Certain Forms of Tuberculosis with a Combination of Prednisone (or Hydrocortisone) and Antibiotics

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Introduction

A study of the pharmocodynamic effects of rapid infusions of para-aminosalicylic acid (PAS) (Fortier and Favez, 1952) had led to the use of cortisone in the treatment of clinically and radiologically recent pneumonic pulmonary tuberculosis (Delaloye and Favez, 1953).

Rapid infusion of PAS[1] in the treatment of active tuberculosis of the lungs has caused radiological improvement which was both more rapid and more extensive than that obtained with antibiotics alone (Favez et al., 1956, A).

Rapid infusion was followed by copious early excretion of free PAS in the urine. The efficacious blood level (above 2 mg./100 ml.) is maintained only half as long as after the usual oral administration. PAS should be in contact with the bacilli for about eight of the 24 hours if bacteriostasis is to be effected. It may therefore be presumed that the unusually rapid absorption of the exudative foci resulting from rapid infusion of PAS cannot be due exclusively to bacteriostasis. These rapid infusions have an adreno-corticotrophic effect (Favez et al., 1954). The superior therapeutic effect obtained by this mode of administration may be correlated with this pituitary adrenal action. It is therefore logical to make an attempt at influencing the pneumonic foci more directly, at least in certain alarming situations, by administration of cortisone, rather than to increase the secretion of this hormone by the intermediary of the hypophysis.

Observations

Forty-two patients have been treated with hydrocortisone and 78 with prednisone since 1952; supplemental findings since obtained have confirmed the preliminary conclusions presented at the time before a meeting of the Société des Médecins de Leysin on October 21st, 1952 (Delaloye and Favez, op. cit.) In the course of the same period similar observations have been

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Cortone, Hydrocortone and Deltacortone graciously supplied by Merck Laboratories, New York, New York.

[1]The terms "rapid infusion" refers to administration, within an hour, of a solution of 18.5 g. PAS sodium in 500 ml. distilled water. The product used was Aminacyl for infusion (Wander). Aseptic preparation of this solution without heating, which permits rapid administration without secondary effects, is described in detail in another publication (Favez et al., 1956 A).

made by Quiring et al., (1953) at Basle, Ovedoff & Bensusan (1953) at Capetown. We have since reported on a new series of cases (Aguet and Favez, 1954), whereas personal observations have been published by Houghton (1954) at London and by Even and Sors at Paris (1954).

The first to mention indications for cortisone in the field of pleurisy and pericarditis were Minet et al. (1952) at Lille. As regards the benefit of corticotherapy in tuberculous meningitis, mention should be made of Shane et al. (1952) in Canada and of Barnard (1953) at Capetown. Numerous publications have since confirmed the above mentioned reports [Favez and Aguet (1956)]. Data on dosage adopted since 1955 according to the experience of Gilbert (1954) are presented in Table I.

A salt-free, high-protein diet was prescribed. Patients treated with pred-

Treatment of the Exsudative Tuberculosis by the Association of Antimicrobial Drugs and Adrenocortical Hormones.

Days	Prednisone mg	Streptomycin Gm	Isoniazid Gm	PAS-Ferrous 18.5 Gm PAS-Na	Clinical and Laboratory Examinations
1		2	0.5		
2		2			weight, BP, fundus oculi, ECG, K, Na, Cl, urea, proteins, glycemia.
3	5	2			
4	10	2			
5	20	2			weight.
6	25	2			
7		2			
8		2			
9		2			weight, BP, K, Na, glycemia.
10		2			
11		2			
12		2			weight.
13		1			
14					
15					
16					weight, BP, K, Na, glycemia.
17					
18					
19					weight.
20					
21					
22					
23					weight, BP, K, Na, Cl, urea, proteins, glycemia.
24					
25					
26		1			weight.
27		2			
28		2			
29		2			
30		2			weight, BP, K, Na, glycemia.
31		2			
32		2			
33	25	2			weight.
34	20	2			
35	10	2			
36	5	2			
37		2			weight, BP, fundus oculi, ECG, K, Na, Cl, urea, proteins, glycemia.
38		2			
39		2			
40		2			
41		2			
42		2			
43		2			
44		1			
45		1			
46		1			
47		1			
48		1			
49		1			
50		1			
51					
52		1			
53					
54		1			

25 mg/Day

1 Gm/Day

0.5 Gm/Day

and so on

TABLE I

nisone received normaily salted food. The protein supply was supplemented with amino-acids in the form of Nesmida broth twice daily.

Routine clinical and laboratory examinations included determination of the temperature, body weight, fluid and compound balance, arterial pressure, Mantoux reaction, radiographic and tomographic findings, examination of the fundus of the eye, determination of bacilli in the sputum, gastric juice and urine, by culture and inoculation into guinea pigs, sensitivity tests, determination of the blood protein, salt and potassium level, electrophoresis, haematological examinations, blood coagulation tests, thrombelastography in some cases, ECG and liver function tests. Only pathological findings are mentioned.

Overall Results

a) *Clinically and radiologically fresh pulmonary tuberculosis (108 cases)*

One hundred and one patients[1] (including one suffering from meningitis with coma, one with meningitis and renal tuberculosis with coma and six with diabetes) were given combined treatment with hydrocortisone or prednisone and antibiotics. In all cases the pneumonic foci were absorbed completely or nearly so within four to eight weeks. Trabecular opacities and certain nodular changes as a rule remained. The cavities often remained unaltered during hormonal treatment and did not close until in the course of the following month. Seven patients, including one who also had diabetes, did not receive hydrocortisone until after having treatment by antibiotics and chemotherapy for 10 days (one case), three weeks (two cases), one month (one case) and three months (two cases). In the last four cases the lesions showed gradual aggravation until cortisone treatment was started. The radiological picture showed moderate improvement in two and considerable improvement in two other cases. The two affected with meningitis and in coma at the time of admission returned to normal psychical condition within less than a week. Inoculation into guinea pigs of cerebrospinal fluid (and in one case of urine) had negative results at the end of two to four months. Guinea pig inoculations and cultures made with material from sputum and gastric juice were negative in all cases from the fourth month of treatment on.

b) *Pulmonary tuberculosis in which the radiological findings show lesion changes adjacent to pneumonic foci (12 cases)*

Seven patients were given combined treatment with hydrocortisone and antibiotics. In two, the radiological improvement was poor and concerned only the apparently exudative factors. In the remaining five no improvement was seen. Five received hydrocortisone only after treatment with antibiotics and chemotherapeutics for one month (two cases) or two months (three cases). Only one of these, who was also suffering from diabetes, showed marked improvement; the opacities showed gradual spread until cortisone treatment was instituted.

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[1]Twenty-three of these showed pulmonary tuberculosis of a miliary type.

Case 1: G. R., a man, aged 64, admitted August 5, 1952, with bilateral, grossly confluent pulmonary foci, predominant on the right (Fig. 1), and specific ulcerative laryngitis. He is cyanotic, dyspnoeic, adynamic and aphonic. The body weight is 32.2 kg. for a height of 5 ft. 2 in. Temperature 39.3° C. Tubercle bacilli are found in the sputum. Average erythrocyte sedimentation rate 47.5 mm./hour; blood pressure 100/75 mm. Hg.; Kolmer-Meinicke reaction weakly positive. Normal ocular fundus. Treatment by intravenous administration of INH (200 mg. daily) is instituted immediately. The general condition deteriorates in the course of three subsequent weeks. Pulmonary lesions spread and spontaneous pneumothorax is seen on the left (Fig. 2). Treatment with cortisone and antibiotics is started. X-ray films a month later show considerable regression of pathological changes (Fig. 3). General findings on discharge (July 13, 1953): the voice is normal, and the pulmonary tuberculosis is stabilized (Fig. 4). Body weight 43 kg. Temperature normal. Repeated cultures and inoculation into guinea pigs show that no tubercle bacilli are present in the sputum. Erythrocyte sedimentation rate 17 mm./hour. The ocular fundus is normal.

Case 2: B. G., a man, aged 39, admitted on January 10, 1953 with bilateral, nodular, infiltrative diffuse pulmonary tuberculosis. He is cyanotic, dyspnoeic, and adynamic. The body weight is 60.3 kg. for a height of 5 ft. 9¾ in. Temperature 39.2° C. Tubercle bacilli present in the sputum. Blood pressure 100/50 mm. Hg.; average erythrocyte sedimentation rate 55 mm./hour. Normal ocular fundus. Normal bronchoscopic findings. Treatment with cortisone and antibiotics is instituted immediately and continued for two months. Radiological evidence of the pulmonary foci disappears after two months.

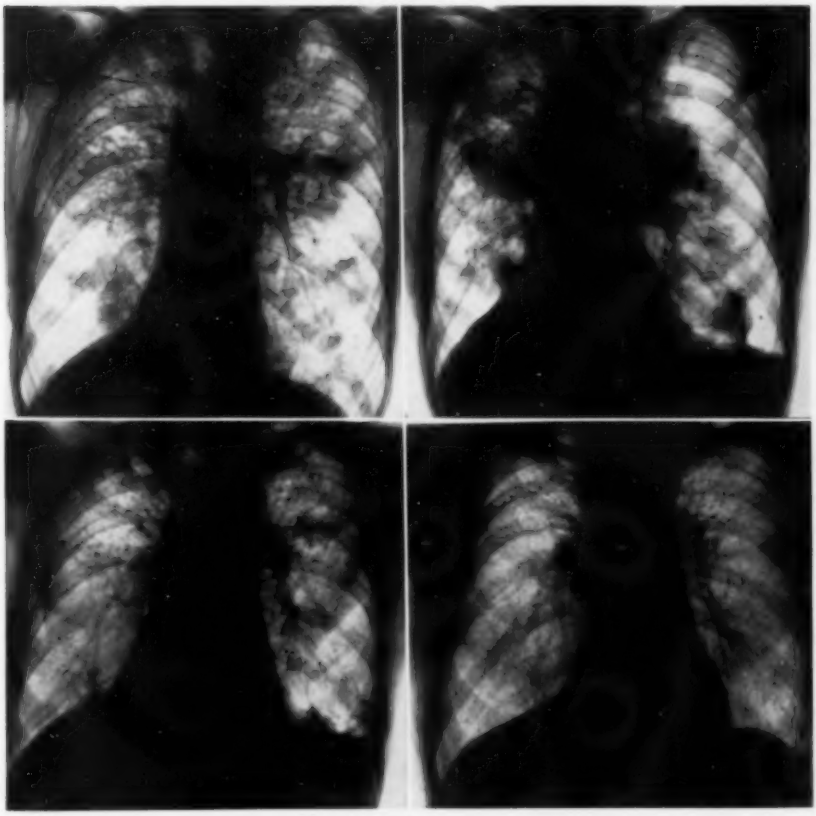

Fig. 1

Fig. 2

Fig. 3

Fig. 4

CASE 1

General findings at discharge (August 7, 1953): the pulmonary features are practically normal. Repeated cultures and guinea pig inoculations show that no tubercle bacilli are present in the sputum. The average erythrocyte sedimentation rate is 2 mm./hour. Normal ocular fundus. Weight 58.5 kg.

Case 3: L. E., a man, aged 51. Admitted on March 5, 1953 with bilateral nodular infiltrative diffuse pulmonary tuberculosis. Urinary tuberculosis and tuberculous meningitis. He is unconscious and in a state of alcoholic cachexia. His condition precludes determination of height and weight. Temperature 38.2° C. Average erythrocyte sedimentation rate 10.5 mm./hour. Blood pressure 110/70 mm. Hg.; tubercle bacilli present in sputum. Thymol 14. Pathological galactosuria test. Ocular fundus: exudative chorioretinitis. Treatment with cortisone and antibiotics is instituted. The pulmonary picture has considerably improved six weeks later and his general condition is more favourable. Examination of the ocular fundus reveals almost complete absorption of the exudative chorioretinitis without pigmentary sequelae. Cerebrospinal fluid (initial values) cytology: five lymphocytes/cu. mm. (8); chloride 416 mg./100 ml. (403; glucose 58 mg./100 ml. (45), proteins 30 mg./100 ml. (42); colloidal gold 12 x 0 (111122100000); pressure 10 cm. H2O (15). Queckenstedt sign normal on both sides. Guinea pig inoculations negative. Discontinuation of cortisone treatment is followed by a relapse of nodular infiltrations of the lungs. The cerebrospinal fluid shows pathological values again, although guinea pig inoculations remain negative. Treatment with cortisone and antibiotics is resumed; all pathological changes have disappeared after a month. The pulmonary picture is normal on discharge (June 23, 1954). The cerebrospinal fluid is normal and guinea pig inoculations are negative. Urine: negative inoculation. Repeated cultures and guinea pig inoculations show that tubercle bacilli are no longer present in the sputum. Temperature normal. Average erythrocyte sedimentation date 14 mm./hour. Body weight 72 kg. Normal ocular fundus. Serum hypoproteinaemia remains (5 Gm./100 ml.). Limited ataxia is shown; he tends to walk with legs spread.

Case 4: P. C., man, aged 40, admitted on May 28, 1953 with nodular confluent foci bilaterally in the upper lobes. Comatose state due to acute tuberculous meningitis. Breathing of the Cheyne-Stokes type. Determination of weight and height not possible. Temperature 37.5° C. Tubercle bacilli in the sputum. Average erythrocyte sedimentation rate 34.5 mm./hour. Blood pressure 135/90 mm. Hg.; normal ocular fundus. Cerebrospinal fluid (cisternal puncture): 70 lymphocytes and 20 polymorpholeukocytes per cu. mm. Chloride 362 mg./100 ml.; glucose 32 mg./100 ml.; protein 55 mg./100 ml. Guinea pig inoculations positive. Treatment with cortisone and antibiotics is started immediately; in addition, 50 mg. INH is administered three times a week by intraspinal injection. He completely regains consciousness within a week, but suddenly shows total paralysis of the left third and fourth cranial nerves. Paralysis shows gradual regression. Slight impairment of coordination is associated with lack of periosteal reflexes in the right arm and generalized hyper-reflexia of the tendons. Lasegue's sign weakly

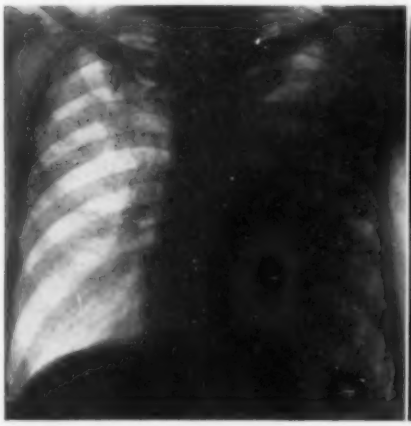

FIGURE 5

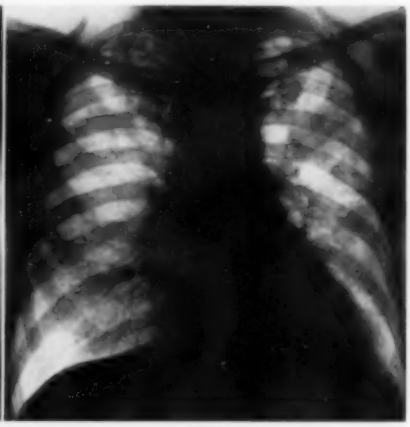

FIGURE 6

CASE 6

positive on both sides. After two months, repeated cultures and guinea pig inoculations show that tubercle bacilli are absent from the sputum. Cerebrospinal fluid: 33 lymphocytes and three polymorpholeukocytes per cu. mm.; chloride 412 mg./100 ml., glucose 41 mg./100 ml., proteins 110 mg./100 ml. Negative guinea pig inoculation. Normal ocular fundus. X-ray findings are satisfactory on the day of discharge (January 21, 1954). Cerebrospinal fluid normal. Guinea pig inoculations negative. Body weight 72.2 kg. as against 57.8 kg. immediately before admission. Average erythrocyte sedimentation rate 21 mg./hour.

Case 5: C. M., woman, aged 40, admitted on November 23, 1953 with tuberculous pneumonic infiltrations in the left upper lobe. The general condition is poor. Body weight 50.1 kg. for a height of 5 ft. 6 2/5 in. Temperature 39° C. The sputum contains tubercle bacilli. Average erythrocyte sedimentation rate 37 mm./hour. Blood pressure 100/70 mm. Hg. Treatment with hydrocortisone and antibiotics is started. A month later the parenchymal opacities have cleared and two months later the pulmonary condition is satisfactory. At discharge (March 31, 1954) tubercle bacilli are absent from gastric lavage, repeated cultures and guinea pig inoculations. Erythrocyte sedimentation rate normal. Normal ocular fundus.

Case 6: P. M., man, aged 54, admitted on March 22, 1955 with pneumonic infiltration on the left lung; cavitation of both upper lobes (Fig. 5). Recent anteroseptal heart infarction; Buerger's disease; diabetes (controlled by 25 U. insulin daily). Normal temperature. Body weight 58.8 kg. for a height of 5 ft. 7 3/5 in. The sputum contains tubercle bacilli. Erythrocyte sedimentation rate 24 mm./hour. Blood pressure 135/80 mm. Hg. Blood sugar level 131-225 mg./100 ml. Slight glucosuria. Abnormal galactose test (normal bromsulphalein test). Van den Bergh test: indirect 0.9 mg./100 ml.; direct slightly positive. Nearly normal ocular fundus. Electrocardiogram findings: typical aspect of recent anteroseptal infarction. Bronchoscopy: numerous secretions in the left bronchial tree of which the mucosa is slightly hyperemic. Hydrocortisone treatment with streptomycin and glucuronolactone-hydrazone is started and continued for two months. The left pneumonic infiltration has been cleared, but the cavitation is still visible (Fig. 6). During hydrocortisone treatment the daily dose of insulin is increased to 50 U. After discontinuation of hydrocortisone treatment, further treatment consists in streptomycin administration, rapid infusion of PAS and INH.

General findings at discharge (September 23): normal temperature; body weight 64.3 kg.; repeated cultures and guinea pig inoculations show that the sputum contains no tubercle bacilli. Average erythrocyte sedimentation rate 34.5 mm./hour. Blood pressure 145/80 mm. Hg. The radiological aspects of the tuberculosis are quite satisfactory. The diabetes no longer requires insulin. Electrocardiogram aspects as usual:

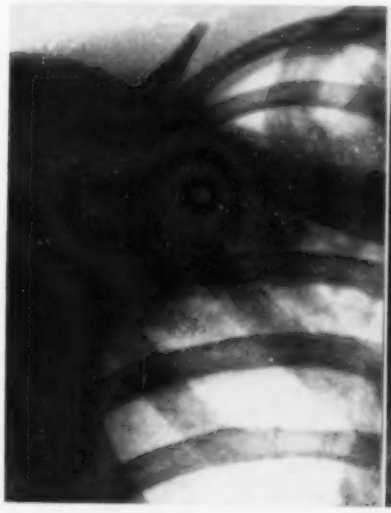

FIGURE 7

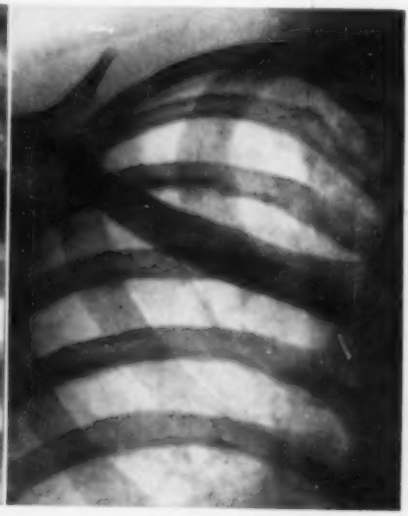

FIGURE 8

CASE 7

in such cases. Buerger's disease shows considerable improvement although oscillographic curves are flat. This condition is favorably influenced by the hydrocortisone. The ocular fundus is unchanged.

Case 7: B. Y., a woman, aged 19, admitted on June 6, 1955 with infiltration in the right upper lobe (Fig. 7). Tuberculous laryngitis confirmed by biopsy. No bacilli in the sputum (cultures sterile). Normal temperature. Body weight 61.2 kg. for a height of 5 ft. 7 3/5 in. Average erythrocyte sedimentation rate 84 mm./hour. Blood pressure 120/70 mm. Hg. Ocular fundus normal. Bronchoscopy: slight hyperemia of the mucosa of right upper bronchus which contains some secretion. Hydrocortisone and antibiotics are given. The right upper lobe has cleared after a month (Fig. 8). The laryngitis has almost disappeared. General findings at discharge (September 22): normal temperature, body weight 70.6 kg. No tubercle bacilli in the sputum as shown by repeated cultures and guinea pig inoculations. Average erythrocyte sedimentation rate 10.5 mm./ hour. Blood pressure 120/70 mm. Hg. Normal ocular fundus. Minute radiological sequelae (tomogram Sept. 20th).

Case 8: R. G., man, aged 16, admitted on June 25, 1955 with pneumonic infiltration of the left upper lobe; nodular infiltrations in both apices with a cavity in the right apex (Fig. 9). Normal temperature. Body weight 54.5 kg. for a height of 5 ft. 8 4/5 in. Sputum contains tubercle bacilli. Average erythrocyte sedimentation rate 10 mm./hour; blood pressure 135/90 mm. Hg. Bronchoscopy: swelling and hyperemia of the mucosa of the left bronchial tree (biopsy: no tuberculous tissue). Treatment with antibiotics and prednisone (25 mg. daily) is started. Normal diet (salt not forbidden); no water retention. The left upper lobe clears a month later (Fig. 10). The cavity is still present, but closes in the course of the second month. General findings at the end of November: body weight 60.8 kg.; temperature normal; no tubercle bacilli in the sputum as shown by repeated cultures and guinea pig inoculations. Average erythrocyte sedimentation rate 3.5 mm./hour; blood pressure 135/75 mm. Hg.; normal ocular fundus.

Case 9: B. H., a man, aged 45, admitted on September 20, 1955 with infiltration of the right upper lobe. Temperature 38.9° C. Body weight 49 kg. for a height of 5 ft. 6 4/5 in. Sputum contains tubercle bacilli. The average erythrocyte sedimentation rate is 15 mm./hour; blood pressure 110/65 mm. Hg. Normal ocular fundus. Bronchoscopy: moderate secretions in the posterior bronchus of the right upper lobe. Hydrocortisone

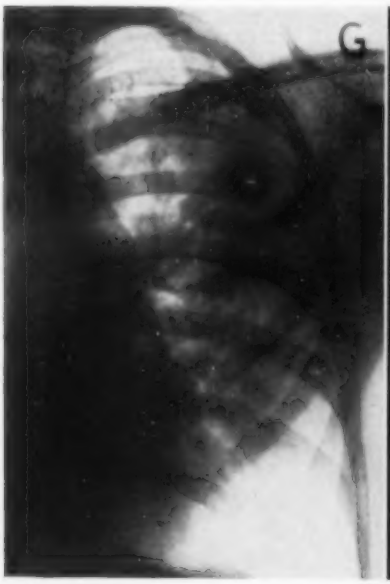

FIGURE 9

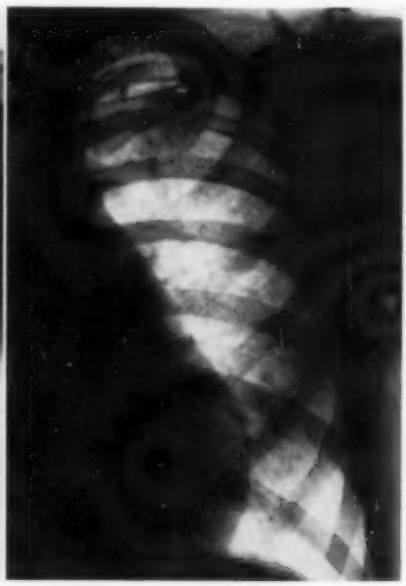

FIGURE 10

CASE 8

and antibiotic treatment is instituted. The right upper lobe clears after a month. Discontinuation of hydrocortisone treatment is followed by hypopotassaemia (9 mg./100 ml.), hyponatraemia (295 mg./100 ml.), hypoproteinemia (4.2 Gm./100 ml.); electrophoresis (in per cent); albumin fraction 42.8; alpha$_1$-globulin 9.7; alpha$_2$-globulin 12.4; beta-globulin 12.9 and per cent gammaglobulin 22.2. Severe pain in the muscle of the legs and phlebitis. Complications are gradually overcome. General findings at the end of November: weight unchanged; normal temperature; sputum still contains tubercle bacilli. Four months later the lung conditions are satisfactory.

Case 10: E. G., man, aged 26, admitted on September 17, 1955. Left-sided pneumonic pulmonary tuberculosis. Temperature 39°C. Body weight 70.1 kg. for a height of 5 ft. 10 4/5 in. Tubercle bacilli in the sputum. Average erythrocyte sedimentation rate 24 mm./hour; blood pressure 125/70 mm. Hg. Normal ocular fundus. Bronchoscopy; hyperemia of the mucosa of the left bronchial tree which contains numerous secretions. Hydrocortisone and antibiotic treatment is started. Defervescence after three days. The left lung is clear after six weeks. General findings at the end of November: body weight 74.5 kg.; normal temperature. Sputum contains no tubercle bacilli as shown by repeated cultures and guinea pig inoculations. Erythrocyte sedimentation rate average 9 mm./hour; blood pressure 140/80 mm. Hg.; normal ocular fundus.

Discussion

Studies made of the properties of cortisone used in the field of tuberculosis are left undiscussed here (Sourdat, 1952; Lurie, 1955; Favez & Aguet, 1956; Aguet & Favez, 1956). However, a survey of the pathological anatomical aspects makes it possible to explain to some extent the discrepancies between earlier assumptions and our own observations.

A brief study of the inflammatory reaction in tuberculosis should permit us to demonstrate that the therapeutic use of cortisone is justified in selected cases of tuberculosis.

It is generally known that tuberculosis enters into the category of inflammatory affections, that is to say, a degenerative stage is followed by an exudative stage, which in its turn may or may not be followed by a proliferative stage. Aschoff's 'lesional dualism', which maintains the existence of two types of tuberculosis—one productive and the other exudative—has been discarded.

The stage of pulmonary degeneration will be left undiscussed; its demonstration is very difficult indeed. Exudation, however, is of great importance; the spongy structure and the rich blood supply of the lungs sometimes permit rapid and extensive invasion of the exudate. The exudate of tuberculous alveolitis is polymorphous, i.e. it is often fibrinomacrophagic or purely fibrinous and exceptionally purulent. The nature and quality of the exudate are determined not only by the intensity of the infection, but also by the specific allergic reactivity of the body. The inflammatory response during the exudative stage is not specific and non-mutilating. The broncho-alveolar structure is intact and *restitutio ad integrum* is therefore possible.

The condition is changed by the occurrence of caseation; caseation is a true necrosis which may leave the alveolar structure intact but which more frequently results in permanent mutilation (of the area affected). Caseation, whether mutilating or not, always leads to a series of proliferative reactions originating in connective tissue, of mesenchymal or reticular origin: the appearance of epithelioid cells, giant cells (largely from the reticulo-endothelial system), lymphocytes and collagen fibers which may iso-

late the caseous lesion. This connective tissue reaction results in the formation of cicatricial tissue which may secondarily calcify or even ossify. There is no constancy, however, in this relatively favorable evolution. Sometimes the caseous material may soften and liquefy for some obscure reason. The formation of cavities and bronchogenic dissemination, facilitated by the canalicular structure of the lungs, is caused by liquefaction. This brief analysis warrants the conclusion that the prognostic evaluation of the severity of pulmonary tuberculosis primarily depends on the following data:

1) the extent of the initial exudative process;
2) the early caseation which is responsible for mutilating lesions (occurring before absorption of the exudate is possible);
3) an insufficient reaction of the connective tissue preventing isolation and cicatrization of the caseous lesion.
4) the liquefaction of the caseous material which gives rise to cavitation and bronchogenic dissemination.

It should be borne in mind that, regardless of the stage of tuberculous inflammation involved, its intensity and quality are not dependent exclusively on the number of bacilli in the lesion. The nature of the reactions depends to a considerable extent on the allergic reaction, the immunity acquired in the course of the inflammation (infection) and natural immunity. This is illustrated by the predominant importance of allergy in the formation of such varied lesions as pure fibrinous alveolitis, caseous necrosis and perifocal inflammation.

An analysis of the possible effect of cortisone on these four aggravating factors seems to lead to the following conclusions:

1) Menkin (1956) has shown that it acts by inhibition of leucotoxin and his most recent works seems to prove that ACTH acts in a similar direct manner by inhibiting the production of exudin in late stages of an acute inflammation (acid exudate). Experimental data tend to confirm this anti-exudative effect of cortisone in cases of tuberculous inflammation.

2) Cortisone is equally important during the proliferative and the healing stage. It inhibits phagocytic activity and the proliferation of fibroblasts *in vitro* and *in vivo*, and reduces their collagen fiber production. In this manner it inhibits the progress of fibrosis and the formation of granulation tissue; it retards the cicatricial process. It does not affect fibrous tissue, whether normal or tumorous. It inhibits vascular proliferation which is of greater importance in the healing process. Also, it alters the nature of the collagenous substance by causing polysaccharide changes.

3) The anticicatricial activity of cortisone constitutes an untoward effect in tuberculosis because it inhibits the reactions of the connective tissue which permit the isolation of caseous matter and the healing of lesions.

4) Experimental pathology has yet to provide further data on the activity of cortisone as regards caseation and subsequent caseous changes. In this respect, too, it appears to have an unfavorable effect.

In conclusion, it should be pointed out that the evolution of tuberculous foci in the same lung may differ from one point to another. The term

'autonomie évolutive' (Canetti) would seem to be suitable here. The time element in the appearance of the proliferative and healing stage is variable. It may never be completely attained: caseous lesions may persist for years without being completely encapsulated. Clinical and radiological examination often fail to reveal the pathological condition of a number of lesions.

The various factors discussed enable us to understand the divergent opinions on the effects of cortisone on pulmonary tuberculosis. They explain the success obtained in highly exudative severe cases of tuberculosis and, on the other hand, the failures and aggravations seen particularly in those forms in which fibro-caseous lesions dominate the clinical picture.

Apparent recent pneumonic foci are nearly completely absorbed within the first four to eight weeks under prednisone treatment. Those lesions that have already undergone some degree of connective tissue organization are relatively refractory. Cavities as a rule do not close until prednisone treatment is stopped in favor of antibiotic treatment. The functional isolation of the cavities during the course of the hormonal treatment is explained by the biological properties of the cortico-steroids and discussed in another paper (Aguet and Favez, op. cit.). Large dosages of SM and INH have been used at the onset of cortico-steroid treatment (resorption of exudate containing bacilli) and after it has been stopped (at this time capillary walls and fundamental substance have recovered original permeability and bacilli have multiplied in lesions) (Lurie, op. cit). Two developmental stages may be distinguished, viz.: absorption of the exudative foci, followed by closure of cavities and gradual regression of nodular elements and gradual or no regression of trabecular changes. The sequelae of an eventual bacillary spread are not observed. They have been studied by guinea pig inoculation (urine), examination of the ocular fundus and thoracic x-ray films regularly during and following hormonal treatment. One patient transiently showed complications due to cortisone treatment (Case 9). One, suffering from longstanding tuberculosis, died nine days after discontinuation of cortisone treatment showing symptoms of acute right heart insufficiency. Hydrocortisone seemed to be responsible for this fatal issue. Autopsy showed thrombosis of the left inferior pulmonary artery. The patient had a haematemesis a few weeks before admission. He was an alcoholic.[1]

Diabetes constitutes no contra-indication to cortisone treatment; however, daily insulin dosage should be adapted for the duration of cortisone treatment. Water retention did not occur[2].

Of the 12 cases of longstanding tuberculosis, five showed a fatal issue three, four and six months, respectively, after cortisone treatment was stopped. The patients died of right-sided cardiac insufficiency resulting

1 In this case, as in Case 9, the patient showed signs of disturbed hepatic function. Data so far obtained seem to suggest that corticosteroid treatment is best refrained from in the presence of disorders of the liver.

2 The two meningitis patients were given rapid PAS infusions at the beginning of treatment, without having oedema. The sodium intake was therefore 3.5 Gm. daily. The absence of water retention is probably explained by the rapid urinary excretion of sodium in these cases (unpublished).

from widespread tuberculosis. The clinical and anatomical findings suggest that cortisone was in no way involved.

The 108 patients suffering from recent pneumonic tuberculosis who were seen since 1952 are all still alive; the first few, including those most severely affected have resumed work and normal social life three years ago. From the human point of view they would have a particularly gloomy prognosis, despite antibiotic and chemotherapeutic treatment. Four patients showed systematic aggravation in spite of specific treatment; radiological improvement was not seen until hydrocortisone was given in addition to antibiotic treatment. It is interesting to note the evolutional autonomy of certain inflammatory processes. The large doses of streptomycin caused no neurological side-effects. It may be stated that hydrocortisone and prednisone had a protective effect owing to its antitoxic properties.

The change in general condition was the more marked if the pneumonic foci were more markedly exudative. The pneumonic foci are considerably less rich in bacilli than the longstanding ulcerative lesions. The improvement in general condition in cases of tuberculosis showing a predominance of longstanding multiple ulcerative lesions was less marked. It may be stated that the disappearance of the major symptoms of acute tuberculosis is dependent on the absorption of the pneumonic exudate. The improvement in general condition may well be correlated with the reduction in the toxine content of the exudate as lesions seem to be isolated during corticosteroid treatment. The patient affected with pneumonic tuberculosis is suffering from an inadequate and dangerous defence reaction rather than from changes directly caused by the bacilli. This conception stands apart from the clinical data in that it is observed in a number of acute infection diseases of varying etiology. Pathological anatomical studies have shown that pneumonic tuberculous lesions include changes of unmistakable etiology and a perifocal alveolitis which, at least at the onset, has no specificity. Regression of pneumonic tuberculous foci commences from the periphery inwards and runs parallel with the disappearance of the chief symptoms of the condition. Menkin (op. cit.) has demonstrated toxic metabolites in the exudates. Reilly and Selye studied the functional sequelae of certain pathological processes. Also, it should be borne in mind that a pneumonic exudate tends to undrego irreversible connective tissue organization. It is therefore logical to make an attempt at reduction of the inflammatory processes in cases of tuberculosis dominated by exudative foci and characteristic of the reactivity of certain subjects.

The late results of cortisone treatment in tuberculosis are not yet sufficiently well known and its disadvantages have not yet been reduced to such a negligible point, that the adrenocortical hormones can be introduced into the routine treatment of circumscribed tuberculosis. In investigations based on the experimental work of Ducommun (1952) we have shown that an anti-inflammatory effect can be produced without hormones by means of association of chlorpromazine and phenylsemicarbazide (Favez et al., 1956, B); the effect thus obtained is usually comparable to that obtained with cortisone.

Conclusions

Acute pneumonic tuberculosis, miliary, serous affections and especially meningitis constitute an indication for prednisone treatment in addition to specific drugs. The results obtained are undoubtedly superior to those seen after antibiotic treatment alone.

SUMMARY

A description is given of 10 cases selected from a group of 120 patients suffering from active pulmonary tuberculosis. These 120 cases were treated with a combination of hydrocortisone (or prednisone), streptomycin and INH. The results obtained in pneumonic tuberculosis, miliary, and tuberculous meningitis were considerably better than those obtained by specific treatment alone. The importance of inflammatory phenomena in pneumonic tuberculosis is discussed.

RESUMEN

Se describen diez casos tomados de un grupo de 120 enfermos de tuberculosis pulmonar activa. Esos se trataron con una combinación de hidrocortisona o prednisona, estreptomicina y Hain. Los resultados obtenidos en formas neumónicas de tuberculosis y en meningitis tuberculosa fueron considerablemente mejores que los obtenidos por los medios específicos solos.

Se discute la importancia de los fenómenos inflamatorios en la tuberculosis neumónica.

RESUME

Les auteurs donnent la description de dix cas choisis parmi un groupe de 42 malades atteints de tuberculose pulmonaire évolutive. Ces cas furent traités par une association d'hydrocortisone ou "prednisone," de streptomycine et d'isoniazide. Les résultats obtenus dans la pneumonie tuberculeuse et dans les méningites tuberculeuses furent considérablement meilleurs que ceux obtenus par le traitement spécifique seul. L'importance des phénomènes inflammatoires dans la pneumonie tuberculeuse est discutée.

ZUSAMMENFASSUNG

Es wird eine Beschreibung gegeben von 10 aus einer Gruppe von 120 an aktiver Lungentuberkulose leidenden Patienten ausgewählten Gruppe. Diese Fälle wurden mit einer Kombination von Hydrocortison oder Prednison, Streptomycin und INH behandelt. Die bei pneumonischen Tuberkulose-Formen und bei tuberkulöser Meningitis erzielten Resultate waren beträchtlich besser als die durch spezifische Behandlung allein erzielten. Es wird die Bedeutung des entzündlichen Phaenomens bei der pneumonischen Tuberkulose-Form besprochen.

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The Diagnostic Significance of Pleural Effusion*

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Introduction

Strictly speaking, the term "pleural effusion" applies to inflammatory exudates within the pleural cavity, usually a result of acute fibrinous pleurisy. Clinically, however, the term includes any fluid within the pleural cavity. Inflammation with fibrin deposition causes thickening and inelasticity of the pleura, often with resultant adhesions and reduced respiratory capacity. Pleuritic type pain results from the stimulation of pain fibers located exclusively within the parietal and diaphragmatic pleurae. As effusion proceeds, fluid separates the pleural surfaces, decreases the friction, and lessens the pain.

Normally, intrapleural pressure varies from minus 14 centimeters of water during inspiration to minus 8 during expiration and therefore is subatmospheric at all times. This pressure is important in the intrapleural transudate formation seen with pulmonary vascular stasis. With effusion, fluid volume causes pressure on and partial collapse of the lung, resulting in decreased negative or actual positive intrapleural pressure. The pressure of the fluid will cause it to lie in the bottom of the pleural cavity and to change in position with body movements. With air present above the fluid, the change is instantaneous and fluid movement can often be heard (Hippocratic succussion). Increased fluid viscosity as well as lack of air in the pleural space causes slower fluid changes with position. Occasionally the weight of the fluid will invert the diaphragm so that inspiratory diaphragmatic contraction actually decreases the thoracic volume, and causes retraction of the costal margin.

Etiology

Tuberculosis causes most of the effusions in individuals under 30 years of age while malignant causes become more frequent in later life. In fact, when there is no demonstrable cause for a pleural effusion in a young person, it should be considered tuberculous until proved otherwise.[1] Some feel that idiopathic pleural effusion in any tuberculin positive individual should be considered tuberculosis.[2] Conversely, it is exceedingly rare for the tuberculin reaction to be negative when the pleurisy is tuberculous in origin.[3] Effusion may be present with other pulmonary disease such as primary atypical, streptococcal, pneumococcal and virus pneumonias, pulmonary abscess or infarction, and actinomycosis, as well as with extrapulmonary disease including septicemias, congestive failure and rheumatic fever, renal disease, liver cirrhosis and nutritional deficiencies.

In an evaluation of 436 cases of pleural effusion at the Mayo Clinic

**Third Prize (tie), 1956 Prize Essay Contest, American College of Chest Physicians.

from 1950-1952, over 50 per cent of these effusions were due to neoplasm. Congestive heart failure caused 10 per cent, infections 8 per cent, and 12 per cent were due to miscellaneous causes with 17 per cent of undetermined etiology. However, the authors feel that "a comparison of the causes of pleural effusion in this series with the causes in other series would be of little value, for many variables affect the selection of patients for admission to the various institutions from which groups of cases have been reported."[4]

Diagnosis and Investigation

History, physical examination and general laboratory procedures will reveal the cause of many pleural effusions. Some, however, pose a much more difficult diagnostic problem and one in which pleural fluid aspiration and examination play vital roles.

History: An acute febrile picture with weight loss and pleuritic type pain suggests a pyogenic process rather than chronic tuberculosis. Rapid weight loss as well as recurring effusions suggest malignancy rather than tuberculosis.

Physical Examination: The patient usually lies on the affected side, allowing free expansion of the normal lung. In a series of 436 cases, 50.9 per cent of the effusions were in the right pleural space, 45.2 per cent were in the left pleural space and 3.9 per cent were bilateral.[4] The patient may be dyspneic, and more comfortable sitting upright. Chest movements are diminished on the affected side with respiration. The classical findings over the area of effusion include diminished-to-absent breath sounds, dullness to percussion with occasional mediastinal shift and diaphragmatic depression. The percussion note above the fluid may be tympanitic, so-called Skodiac resonance. A friction rub may precede the effusion but usually disappears after the latter develops.

X-Ray Films: Except for blunting of the costophrenic angle, chest x-ray films may be negative for days or weeks until the fluid rises above the dome of the diaphragm. The amount of pleural fluid must be about 300 cubic centimeters to be radiologically visible in the upright position. The shadow of the fluid may be observed to shift with different positions. Lateral and oblique films may be required for the fluid visualization.

Pleural Fluid Examination: Routine examination should include general appearance, specific gravity and quantitative protein for transudate-exudate determination, cell count and differential, and gram plus acid fast stains for bacteria. Cell block and Papanicolaou smear for malignant cells as well as culture for tuberculosis should be performed.

1. *General Appearance:* This serves to separate empyema and chylous fluids as well as hemorrhagic effusions. Both color and opacity should be recorded.

2. *Transudates and Exudates:* Transudate characteristics are approximately those of a capillary filtrate. By definition transudates have a specific gravity under 1.015, less than 3 gram per cent of protein, contain few cells and do not clot. Exudate cell counts vary from 100-10,000 white

cells per cubic millimeter, often clot and have a specific gravity and protein content above 1,015 and 3 gram per cent respectively. Exudates are formed as a result of injury to the capillary wall resulting in increased permeability with subsequent protein leakage out of the vascular space.

Nephritis, cardiac decompensation, liver cirrhosis and nutritional deficiency are associated most often with transudates. Exudates are most often due to acute or chronic inflammation and neoplasia. Several factors which modify the process of transudation or exudation are rate of capillary filtration, venous pressure, oncotic pressure, heat, interference with capillary fluid reabsorption or lymphatic drainage, and exercise.[5] In one series pleural fluid was obtained from 50 per cent of several hundred presumably healthy Japanese soldiers with an increase of fluid recovery to 70 per cent after exercise and a decrease to 29 per cent with previous rest. In these experiments the puncture site was the posterior axillary line at the ninth or 10th intercostal space. The amount of fluid obtained varied from a few bubbles up to several cubic centimeters.[17]

Specific gravity, in general, is an inaccurate device for determining "infected from non-infected" fluids (transudates vs. exudates). It is markedly affected by temperature, and lowering serous fluid from body to room temperature may increase its specific gravity by as much as .010, using hydrometer measurement. Most hydrometers (urinometers) are corrected to a temperature of 60°Fahrenheit (15.5°Centigrade). The range of specific gravities is also wide for any given condition:[6]

Condition	Number of Cases	Average Specific Gravity	Range
Cardiac	313	1.010	10 per cent over 1.016
Tuberculous	290	1.020	10 per cent under 1.016
Neoplastic	123	No peak	1.010-1.020
Pulmonary Infarction	100	1.019	1.010-1.042
Cirrhotic	21	1.010	1.004-1.019
Nephrotic	16	1.006	1.001-1.008

Protein content is roughly proportional to specific gravity of a fluid, with a range in pleural fluids from normal persons of 1.38 to 3.35 and an average of 1.77 gram per cent.[6, 17] Clotting affects the protein content only slightly, and has no effect on specific gravity.

3. *Character of Fluid:*

a. *Hemorrhagic fluid:* To call an effusion hemorrhagic, an evenly mixed bloody tint should be seen macroscopically. Needle trauma produces an unevenly mixed aspirate, with only the first (or last) few cubic centimeters of fluid bloody. A red cell count of 5000-6000 per cubic millimeter will impart a rosy tint to the fluid. Many simple serous effusions of inflammatory origin contain some red cells microscopically. If pure blood rather than serosanguinous fluid fills the cavity, the term

hemothorax is used. Serosanguinous fluid is most characteristic of carcinoma although it may be found in tuberculosis and even, rarely, in congestive failure.[4]

In one series of 120 cases of hemorrhagic effusion at a general hospital 65 per cent of the cases were due to malignant neoplasms. A miscellaneous group of inflammatory conditions produced 21 of the 120 effusions of which eight were tuberculous. Pulmonary emboli caused 10 of the 120 cases. The remainder of the cases were divided among pelvic fibromata (uterus and ovary), leukemia and Hodgkins, uremia with cardiac failure, and five of the cases were classified "cause undetermined".[7]

b. *Purulent fluid:* Inflammatory exudates from tuberculosis contain up to 90 per cent lymphocytes while polymorphonuclear leukocytes predominate in the bacterial pneumonias. However the range of variation is wide; in one series of 229 tuberculous effusions, nine cases contained over 50 per cent polys.[6] White cell counts in neoplastic effusions vary from 60-20,000 per cubic millimeter with lymphocytes predominating.[7]

If the fluid is opaque, empyema is said to be present, whereas with translucency the terminology is usually "purulent pleural effusion." Empyema is less often seen today due to the widespread use of antibiotics and sulfas in the treatment of acute pulmonary tract infection. Formerly, this condition occurred in 5 to 6 per cent of pneumococcal pneumonias and was frequently a complication of respiratory hemolytic streptococcal infections.

c. *Milky fluid:* This represents lymphatic obstruction with escape of chyle. Ether extraction differentiates chylothorax from the haziness common with transudates, for example those associated with cirrhosis and nephrosis. In cases unassociated with obvious traumatic rupture of the thoracic duct, the commonest causes of milky fluid are neoplasm, tuberculosis, nephrosis and cirrhosis, in decreasing frequency. Abnormal lipid content has no effect on specific gravity.

Findings in Various Diseases

Tuberculosis: The usual explanation for tuberculous pleurisy with effusion is on the basis of allergy, the tissues having become sensitized to tuberculoprotein during the first three to seven weeks after the initial invasion of the organisms. In persons without demonstrable clinical pulmonary tuberculosis the mechanism is usually subpleural lesions resulting from localization of tubercle bacilli promptly after their first invasion.[8] Tuberculosis is the commonest cause of infectious effusions.

The fluid is usually serous, occasionally serosanguinous and rarely frankly bloody. Translucent fluids do not usually contain enough organisms to be demonstrable by staining; therefore culture and/or guinea pig inoculation must be employed. This should be done from sediment of large (100-500 cubic centimeters) amounts of fluid, which results in detection of organisms in 70 per cent of primary effusions in young people.[9] Pleural fluid sugar is far below blood sugar in tuberculous pleurisy and is also lowered in most exudates. Gastric washings and

sputum should also be examined and tuberculin testing should be performed. Pleural fluid leukocytosis is rare in tuberculosis, even with empyema. The white cell count is frequently below 1000 per cubic millimeter. Some 40 per cent of unexplained effusions will be associated with demonstrable tuberculosis within five years.

Diagnostic biopsy of a 1.5X 3 centimeter area of parietal pleura is of especial value where bacteriological methods do not establish a diagnosis, and is without particular danger.

Carcinoma: Generally, pleural effusions due to neoplasm are large with from one to 10 liters frequently removed by aspiration. Tumor cells are found in the pleural fluid of about one half of the cases of neoplasm regardless of whether the fluid is serous or hemorrhagic.[7] Both paraffin cell block and Papanicolaou smear may be employed and there is some evidence that repetition of cell block examinations significantly increases the percentage of diagnoses. Negative findings are not sufficient to rule out malignant effusion although false positive results occur in up to 3 to 5 per cent of cases.[11] Highly atypical cells may be present in fluids that have been standing for a long time; therefore this finding does not always mean malignancy

Neoplastic pleural fluid characteristically continues to form after aspiration. X-ray film after air insufflation may reveal tumor nodules on the pleura.

Carcinoma of the bronchus is the most common type of tumor, with carcinoma of the breast second. The only primary tumor of the pleura, mesothelioma, is rare.

Acute Infections: The effusion is usually an exudate, accompanied by a polymorphonuclear leukocytosis.

Congestive Failure: Effusion is on the right side in 55 to 70 per cent of cases and is usually a transudate accompanied by other signs of decompensation.

The pathogenesis of effusion in congestive failure as well as the right-sided location of most effusions has been attributed to various mechanisms. One explanation is that pressure on the root of the right lung and azygos vein by an enlarged right auricle causes right-sided effusions.[12] All in all it seems that the causes of unequal pleural effusion in heart failure have yet to be elucidated.[13]

Rheumatic Effusions: These occur in a small fraction of patients with acute rheumatic fever. The fluid has a high specific gravity, tends to bloodiness, and has a rapid clotting time.

Treatment

Bed rest is the first fundamental of treatment. Aspiration of the effusion restores non-expanded lung to functioning, thereby preventing pleural adhesions from forming and aiding in localization of the infection by the pleura itself.

Many effusions resorb spontaneously on bed rest, especially if small. Streptokinase and streptodornase have been injected intrapleurally causing lysis of fibrinous adhesions and cellular debris. These agents have

been most extensively used in the treatment of sanguinous effusions where fibrin is the major substrate and in empyema where nucleoprotein constitutes the bulk of the solid sediment.[14]

Injections of radioactive colloidal gold into the pleural cavity have reduced the rate of fluid formation in about 40 per cent of patients with neoplasms. Results have been best with carcinoma of the breast and less effective with bronchogenic carcinoma.[15] The gold implantation selectively irradiates the lining membrane of the serosal cavity without effecting undue radiation to other parts of the body.[16] This method of treatment should only be used where there is free fluid and loculation has been ruled out.

Nitrogen mustard has been injected directly into malignant pleural (as well as into peritoneal and pericardial) effusions with a decreased or eliminated fluid formation in 65 per cent of the patients in one series.[18] The incidence of side effects (leukopenia, nausea and vomiting) was less than with intravenous nitrogen mustard therapy and these effects were mild in nature when they did occur.

Acknowledgment: I am indebted to Dr. Chester L. Plotkin for his helpful suggestions in the preparation of this paper.

SUMMARY

The etiology, diagnosis, investigation and treatment of pleural effusions have been discussed. The frequency of tuberculous origin of so-called "idiopathic pleural effusion" has been reemphasized. Congestive failure, inflammatory processes, and neoplasm are responsible for most of the effusions seen among the general population.

The routine procedures for diagnostic laboratory examination of pleural fluid have been evaluated in the light of present knowledge, with the following general conclusions.

A. General appearance of the fluid identifies empyema, chylothorax, hemorrhagic effusion and traumatic bleeding.

B. Transudate-exudate determinations correlate only generally with the type of process causing the effusion.

C. Clotting of the fluid has little effect on protein content and no effect on specific gravity.

D. Hemorrhagic effusion is due to malignant neoplasm in over 50 per cent of the cases, and tuberculous effusion is not commonly hemorrhagic.

E. Differential counts of the pleural fluid are of most value in differentiating acute pneumonias from tuberculous processes. Polymorphonuclear leukocytes are the predominant cell type in most pneumonias while lymphocytes usually, but not always, predominate in the tuberculous effusions.

F. The tubercle bacillus is often demonstrated by guinea pig inoculation and/or culture, and one or both of these procedures should be part of the routine examination of pleural fluids.

G. Tumor cells are found in about half of the cases of neoplasm, the percentage being somewhat higher in carcinoma of the breast than with bronchogenic carcinoma. False positives occur.

Techniques for diagnostic biopsy of the pleura as well as therapeutic injection of radioactive gold and nitrogen mustard into the pleural space have been discussed.

Examination of the pleural fluid is most valuable in making the definitive diagnosis of tuberculosis by culture and of neoplasm by cell block and Papanicolaou smear. The other procedures involved in determining pleural fluid characteristics have such a wide range of values in any given pathologic condition that diagnosis is, at best, presumptive.

RESUMEN

Se hace una discusión de la etilogía, el diagnóstico, la investigación y el tratamiento de los derrames pleurales. Se recalaca otra vezla frecuencia del origen tuberculoso de las llamadas "pleuresías idopáticas." La insuficiencia congestiva, los procesos inflammatorios, las neoplasias son responsables de la mayoría de los derrames pleurales entre la población en general.

A la luz de los conocimientos actuales se han valorado los procedimientos de rutina en el diagnóstico de laboratorio llegando a las siguientes conclusiones:

A. La apariencia del líquido sirve para identificar el empiema, el quilotórax, el derrame sanguinolento y la hemorragia traumática.

B. Las determinaciones del tipo de exudado o transudado están en correlación sólo de manera general con el tipo de padecimiento que causa el derrame.

C. La coagulación del líquido tiene pocos efectos sobre el contenido de proteína y ninguno sobre la gravedad específica.

D. El derrame sanguinolento es debido a neoplasia maligna en más del 50 por ciento de los casos y el derrame tuberculoso no es comunmente hemorrágico.

E. Las cuentas diferenciales del líquido pleural son del mayor valor para distinguir entre las neumonías aguda y las afecciones tuberculosas. Los leucocitos polimorfonucleares dominan en la mayoría de las neumonías en tanto que los lifocitos generalmente, pero no siempre dominan en los derrames tuberculosos.

F. El bacilo de la tuberculosis a menudo es demostrado por la inoculación o por el cultivo y uno o ambos procedimientos deben formar parte del examen de rutina del líquido pleural.

G. Las celdillas tumorales se encuentran aproximadamente en la mitad de las neoplasis siendo el porcentaje algo más elevado en el carcinoma mamario que en el carcinoma bronquiogénico. Hay también falsos positivos.

Se discuten las técnicas para biopsia diagnóóstica, así como las inyecciones terapéuticas de oro radioactivo, y mostaza nitrogenada en el espacio pleural.

El examen del líquido pleural es lo más valioso para hacer el diagnóstico definitivo de tuberculosis por cultivo y de las neoplasias por los métodos de bloque de celdillas o el frotis de Papanicolaou.

Los otros procedimientos que se usan para determinar las características del líquido tienen valores tan variables en cualquiera condición patológica, que el diagnóstico por ellos cuando más es de presunción.

RESUME

L'auteur envisage l'étiologie, le diagnostic, les recherches complémentaires et le traitement que demandent les épanchements pleuraux. La fréquence de l'origine tuberculeuse des soi-disant "épanchements pleuraux idiopathiques" a été mise de nouveau en évidence. L'atteinte congestive, les processus inflammatoires, et le cancer sont responsables de la plupart des épanchements vus dans l'ensemble de la population.

L'auteur émet un jugement sur les procédés habituels du diagnostic de laboratoire à la lumière de nos connaissances actuelles. Ses conclusions sont les suivantes:

A. L'apparence générale du liquide permet l'identification de l'empyème, du chylothorax, de ila pleurésie hémorragique ou de l'épanchement sanguin d'origine traumatique.

B. Les caractères de transsudat ou d'exsudat ne correspondent que d'une façon très générale aux conditions qui ont déterminé la constitution de l'épanchement.

C. La coagulation du liquide correspond un peu à sa constitution protéinique et n'a pas de rapport avec la gravité.

D. L'épanchement hémorragique est dû à une néoplasie dans plus de 50% des cas; l'épanchement tuberculeux n'est habituellement pas hémorragique.

E. L'examen cytologique du liquide pleural est de grande valeur pour distinguer les pneumonies aiguës des processus tuberculeux. Les polynucléaires sont les types cellulaires prédominants dans la plupart des pneumonies, tandis que les lymphocytes habituellement, mais pas toujours, sont les plus nombreux dans les épanchements tuberculeux.

F. Le bacille de Koch est souvent mis en évidence par l'inoculation au cobaye accompagnée ou non de la culture, et l'un de ces deux procédés devrait faire partie de l'examen de routine des liquides pleuraux.

G. Des cellules tumorales sont trouvées dans environ la moitié des cas de néoplasie, le pourcentage étant quelque peu plus élevé dans les cancers de la paroi thoracique que dans les cancers bronchiques. Des examens faussement positifs ne sont pas exceptionnels. L'auteur discute les procédés de diagnostic par biopsie de la plèvre, ainsi que l'injection thérapeutique d'or radioactif et de moutarde nitrogène dans l'espace pleural.

L'examen du liquide pleural prend surtout de la valeur quand il permet un diagnostic formel de tuberculose par les examens de coupes sériées après inclusion ou de frottis colorés par la méthode de Papanicolaou. Les autres procédés mis en oeuvre pour déterminer les caractères du liquide pleural ont une échelle de valeurs tellement étendue pour un état pathologique donné qu'ils ne permettent, au mieux, qu'un diagnostic de présomption.

ZUSAMMENFASSUNG

Die Aetiologie, Diagnose, Untersuchung und Behandlung von pleuralen Ergüssen wurden besprochen. Die Häufigkeit tuberkulöser Ursachen bei sogenannten "idiopathischen pleuralen Ergüssen" werden neu erlich hervorgehoben. Herzversagen mit Stauung, entzündliche Prozesse und Neoplasmen sind verantwortlich für die meisten in der Gesamtbevölkerung auftretenden Ergüsse.

Die Routine-Massnahmen zur diagnostischen Laboratoriums-Untersuchung pleuraler Flüssigkeit wurden im Licht der gegenwärtigen Kenntnisse ausgewertet mit den folgenden allgemeinen Schlussfolgerungen:

A. Das gewöhnlich Aussehen der Flüssigkeit führt zur Identifizierung von Empyemen, Chylothorax, haemorrhargischem Erguss und traumatischer Blutung.

B. Transudat-Exsudat-Bestimmungen stehen nur ganz allgemein in Beziehung zum Typ des den Erguss bedingenden Prozesses.

C. Die Gerinnung der Flüssigkeit hat wenig Einfluss auf den Proteingehalt und keinen Einfluss auf das spezifische Gewicht.

D. Haemorrhargischer Erguss ist die Folge bösartiger Neoplasmen in über 50% der Fälle, und der tuberkulöse Erguss ist gewöhnlich nicht haemorrhargisch.

E. Differenzier en Zellzählungen aus der pleuralen Flüssigkeit sind von höchstem Wert bei der Abgrenzung akuter Pneumonien von tuberkulösen Prozessen. Polymorphkernige Leukozyten sind der vorherrschende Zelltyp bei den meisten Pneumonien, während die Lymphozyten für gewöhnlich, aber auch nicht immer, bei den tuberkulösen Ergüssen überwiegen.

F. Das Tuberkelbainfection wird oft nachgewiesen durch Meerschweinchenimpfung und/oder Kulturverfahren, und eine oder beide dieser Methoden müssen ein Teil der Routine-Untersuchungen pleuraler Flüssigkeiten sein.

G. Tumorzellen werden in ungefähr der Hälfte der Fälle von Neoplasmen gefunden, wobei der Prozentsatz etwas höher liegt für Carcinome der Brustdrüse als für bronchogene Carcinome. Irrtümlich positive Befunde kommen vor.

Es wurde die Techniken zur diagnostischen Biopsie der Pleura sowohl als auch für die therapeutische Injektion von radioaktivem Gold und Senfgas in den Pleuraspalt besprochen.

Die Untersuchung der pleuralen Flüssigkeit ist besonders wertvoll, um die definitive Diagnose einer Tuberkulose durch Kultur zu stellen und die eines Neoplasmas durch Zellverarbeitung und Ausstrich nach Papanicolaou. Die anderen an der Bestimmung der Charakteristika pleuraler Flüssigkeiten beteiligten Massnahmen besitzen einen so weit gesteckten Wert bei gegebenen pathologischen Umständen, dass die Diagnose bestenfalls eine mutmassliche bleibt.

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Treatment of Pulmonary Hydatidosis

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Little can be said on behalf of the medical treatment of pulmonary hydatidosis. The biological treatment, with an hydatid anatoxin, introduced by Yma Appatie and modified by several other authors (i.e. Calcagno and Manfredi), might prove to be the method of the future, especially in the field of prevention of this disease, but is not effective in its present state of development. Other medical treatments used against hydatidosis in the past, such as antihelminthics, potassium iodide etc. are of no value.

The same is true of the radiotherapic treatment advocated by Holfelder, with the understanding that while x-rays may sometimes kill the parasite, the only way that it can be eliminated is by vomica, which in our opinion is more often a dangerous complication than a cure.

Several of the methods of surgical treatment of pulmonary hydatidosis, such as punctures, intrapleural pneumothorax, paralysis of the phrenic nerve should also be discarded as inefficient or harmful (they too lead to vomica), or both. Thoracoplasty is of no therapeutical value either and may even be harmful.

Removal of the cyst seems to us, along with a vast majority of authors, the only sound treatment of pulmonary hydatidosis. Not only is it the most effective cure, but has also the advantage of permitting a *restitutio ad integrum*, as the hydatid cyst does not destroy pulmonary parenchyma but only distends it. Before endotracheal intubation anesthesia was widely accepted, extirpation of the cyst involved a serious risk, i.e. a formation of an intrapleural pneumothorax. While some authors disregarded this danger, the great majority tried to avoid it by creating adhesions before or during the operation, or by suturing the lung to the wall after the extirpation of the cyst. None of these methods was successful and fortunately, as the threat of intrapleural pneumothorax no longer exists, we can now use simpler and more effective techniques. The one described below is, in our opinion, the best. It has yielded good results in 103 patients operated in the years 1945 to 1951 that are the object of this study. Sixty-three of them had a simple hydatid cyst; 31 had multiple hydatid cysts (20 of them bilateral); nine had complicated cysts, eight of them being opened into the bronchia and one into the pleura.

The average period of hospitalization was, for patients with simple cysts, 10 to 15 days; for those with bilateral cysts 20 to 30 days; and for those with complicated cysts 14 to 20 days. All of the operated patients recovered and did not suffer a relapse in the two years following the removal of the cysts. Postoperative complications were few: one partial pneumothorax that lasted two days and two minor infections with cocci. There was no case of bronchogenic dissemination, nor of sensibilization or anaphylactic shock. The only death was that of a

patient who died from tuberculosis a year after the operation; whether his tuberculosis was in any way relationed with the operation for hydatid cyst was not established.

The technique of extirpation of hydatid cyst that we recommend for all kinds of pulmonary cysts, single or multiple, open or closed, no matter what their size or location,* has its origin in the method of Bird and Lozano which consisted of suturing the lung to the wall after the removal of the cyst. It was adapted to be used with intratracheal pressurized anesthesia by McKay, and Dr. Benzo who used it in Madrid, Spain, modified it further by suppressing the parietal suture of the lung.

A limited thoracotomy, of some 8 to 10 cms. is performed in the zone where the cyst has been previously located. If radiological means are not available or for some reason cannot be used, percussion is helpful in localizing the cyst. Thoracotomy should be done with costal resection, as this helps to later close the pleura properly. (If, in spite of this precaution, it is found impossible to make the closure of the pleura hermetic, it will be necessary to place aspiration tubes in the intrapleural space). Once the thorax is open, the pulmonary parenchyma is punctured with a number 22 needle, until the characteristic "rock water" starts to flow. The needle is left *in situ*, and the pulmonary parenchyma is punctured there with a scalpel. The wound in the parenchyma should be just big enough to allow the passage of the trocar. The trocar, 0.5 cm. in diameter, is connected with an aspiration apparatus, with which as much liquid as possible is drawn. The trocar is then removed and the collapsed membrane appears. It is caught with Duval's forceps in such a way that the orifice left by the trocar in the membrane is closed by the forceps' ends to prevent whatever might be left of the hydatid liquid from spilling. Instead of Duval's forceps, a large trocar, 1.5 cm. in diameter, may be used to obturate the opening left by the first trocar in the cyst. As this trocar, too, is connected to an aspiration apparatus, it removes the empty, or almost empty, membrane. All this, of course, has to be done with the utmost respiratory silence and extreme care in avoiding spilling of the hydatid liquid and, consequently, a contamination. Before closing the thorax, all the bronchi should be checked to see if any of them needs to be sutured, although this is seldom the case.

The former practice to leave a drainage with a rubber catheter, connecting the postcystic cavity with the exterior has been abandoned, because a carefully performed operation does not produce hemorrhage in the cavity. Endotracheal anesthesia with a closed circuit should be the rule; only if absolutely contraindicated because of poor general state of the patient, or for some other reason, local anesthesia with novocaine should be used. After an operation with local anesthesia aspiration tubes should be placed in the intrapleural space, since continuous aspiration is the only way to avoid formation of intrapleural pneumothorax in these cases. The possibility of using local anesthesia in this operation

*It may also be used in some cases of infected cysts in which the symptoms of the infection are not pronounced, although generally it is better in such cases to proceed to the resection of the affected part of the lung.

and the fact that it is not very traumatic reduce the cases in which it is contraindicated to a negligible minimum.** As for the danger of sensibilization, which some authors point out, we believe that it is practically non-existent in a carefully done operation; in fact we did not see a single case of sensibilization in all the patients with hydatidosis studied or observed by us.

Resection of the affected part of the lung is usually indicated in suppurating cysts. In some cases a simple pneumotomy with drainage, without resection, may be indicated; it occurs mostly when the bad general condition of the patient does not permit an operation. According to several authors though, pneumotomy with drainage often gives way to bronchiectasis, which can only be avoided by the resection of the affected part of the lung.

Treatment of Complications of Pulmonary Hydatidosis

The opening of the cyst into the pleura may present itself with or without empyema. In both cases, but most especially in the first one, great quantities of antibiotics should be applied. The choice antibiotics are penicillin, streptomycin, and the wide spectrum ones, most especially those derived from tetracyclin. An extended thoracotomy should be made, removing the cysts from the pleura, aspiring pus, if there is any, and extirpating the remains of the pulmonary cyst which originated this complication. It will be necessary to find out whether there is a bronchial fistula, to suture it, if possible, and if not, to proceed to a resection of the affected part of the lung. Antibiotics should be applied locally, the lung reexpanded, and an intrapleural aspiration installed. Samples of germs present in the cavity will serve to determine the choice of antibiotics to be used after the operation. Should there be a residual empyematic cavity, streptokinase—streptodornase or trypsin may be injected into it to dissolve the fibrine and obtain a good pulmonary reexpansion. In other cases it might be necessary to proceed to a mechanical decortication, with or without thoracoplasty; the very serious cases will have to be treated with a pneumonectomy with an occlusive thoracoplasty —fortunately nowadays these extreme cases are far from frequent.

A vomica should be followed as closely as possible by an operation to extirpate the cyst. If the vomica is abundant and is producing serious asphyxia, it calls for an immediate postural drainage and, as soon as possible, for a bronchoscopy with aspiration of secretions. Hemoptysis may precede a vomica; should it occur, the hematocrit should be reestablished to its normal level and the cyst removed without delay.

Among other complications the secondary bronchogenic infiltration is rather frequent. The only available treatment is the extirpation of the daughter cysts, as well as of that which produced the infiltration. Due to the presence of parasite's remains or, more often, to an infection, the hydatic cavity may persist after the extraction of the cyst or, more commonly, after vomica. If there is no sign of infection, pneumotomy

**Patients allergic to echinococcus may be desensitized by vaccination.

may be tried to remove what is left of the parasite. But this operation only seldom gives satisfactory results, and in some cases it originates other complications. We therefore think that the best treatment in these cases is the resection of the affected part of the lung.

SUMMARY

Pulmonary hydatidosis can at present be only treated surgically. All kinds of cysts, with the exception of the suppurated ones that call for a resection of the affected part of the lung, should be extirpated with the technique described, which is safe and effective.

CONCLUSIONES

Actualmente la hidatidosis pulmonar sólo puede tratarse quirúrgicamente. Toda clase de quistes, con excepción de los supurados que requieren una resección la parte afectada del pulmón, deben extirparse con la técnica descrita que es segura y efectiva.

RESUME

L'hydatose pulmonaire ne peut actuellement être traitée que par la chirurgie. Toutes les catégories de kystes à l'exception de ceux qui sont suppurés et qui demandent une résection de la partie atteinte des poumons devraient être extirpée par la technique décrite par l'auteur, qui se montre à la fois sans danger et efficace.

SCHLUSSFOLGERUNGEN

Pulmonale Hydatidose kann z.Zt. nur auf chirurgischem Wege behandelt werden. Alle Arten von Zysten mit Ausnahme der eitrigen, bei denen eine Resektion der befallenen Lungenabschnitte erforderlich ist, sollten mittels der beschriebenen Technik extirpiert werden, die sicher und wirksam ist.

Osseous Tuberculosis with Concurrent Pulmonary Lesions

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With the discovery of streptomycin by Waksman in 1943, a new era in treatment of tuberculosis made its entrance. Glowing reports of its effectiveness in pulmonary and other types of the disease led us first to conclude that it would wipe out tuberculosis. But the effectiveness in bone and joint tuberculosis was minimal. True, it appeared to slow down the rate of destruction, but it did not reverse the destructive process, nor bring cure to the many involvements of spinal, sacroiliac and peripheral joint tuberculosis. Disappointment was the lot of the orthopedic surgeon, and reliance upon the old rules of treatment was the usual course of procedure.

To briefly paint the background of this previously accepted and undisputed therapeutic regimen, we should recall that arrest of the disease was based upon the evidence that skeletal tuberculosis was almost always a joint region involvement and practically never a destruction of the shafts of long bones. Principles were based on the fact that if motion could be stopped, the disease would become quiescent, and if fusion with complete obliteration of the joint secured, by whatever means, then cure of the disease was possible. Only with the absolutely fused joint was this to be attained. Only the ingenuity of the physician limited the various methods of using splinting, frames, casts, traction, and braces. Improvement required years of patient care. The subsequent surgical procedures of bone grafting, osteotomy etc., to secure solid bony arthrodesis and good functional positions, then became the final problem. The existence of cold abscesses was looked upon with alarm, and aspiration, to relieve the internal tension, and prevent its breaking through the skin, was resorted to, because the formation of a draining sinus with subsequent secondary pyogenic infection was felt to be the cause of the almost invariably fatal "amyloid disease." The statement that "draining the tuberculous abscess frequently signs the patient's death warrant" was quoted in many texts of bone and joint tuberculosis.

This generally was the status of the treatment of osseous forms of tuberculosis in 1946, 10 years ago, when this reported study was begun. The decision to depart radically from these accepted tenets of treatment was based upon the following theoretical thinking:

1. An analysis of reported success and failures of streptomycin of various forms of tuberculosis revealed the success to be largely related to location of lesions as to adequacy of physiologic drainage. For example, laryngotracheo bronchial lesions—with surface drainage easily attained, responded rapidly in comparison with interstitial fibrotic lesions in the pulmonary tis-

Presented at the 22nd Annual Meeting, American College of Chest Physicians, Chicago, Illinois, June 7-10, 1956.

sues. Involvement of kidney, pelvis, ureter and bladder was far more favorably affected than cortical kidney lesions, etc.

2. Lesions which tended to be surrounded by relatively avascular tissues, such as scar masses or large necrotic masses and abscesses, often failed to be favorably affected. This was felt to be a result of inadequacy of blood supply to carry the antibiotic to the active lesion.

In October, 1946 treatment was begun in a series of cases, now totaling 142 patients, representing 194 operations. In a few a single lesion required more than one surgical procedure to secure complete drainage of the lesion. In others, more than one lesion was present, and required multiple surgical procedures. Almost every joint area of the body was represented, including the entire spine, sacroiliac joints, ribs, sternum, and peripheral joints. The principles of therapy gradually devolved themselves to essentially those accepted for many years as basic in the treatment of pyogenic osteomyelitis. The keynote has been the adequate drainage of the entire lesion coupled with antituberculosis drugs. Adequately large incisions and thorough removal of all pus, necrotic and caseous material, loose fragments and sequestra from the region of bone destruction is essential. Gauze packing is placed tightly from the base of the lesion outwards to the skin, and any suturing of the wound is avoided. The lesion and its cold abscess thus becomes converted, after removal of the packing in 12 to 14 days, into a wide funnel shaped, freely draining sinus. No further packing is done. The freely bleeding, granulation tissue lined sinus is allowed to spontaneously close under the influence of the antibiotic and antituberculosis drugs. The healthy healing tract gradually becomes smaller and smaller and closure of the skin is attained in periods varying from a few weeks to a few months in practically all cases. Undue prolongation of the healing is evidence of inadequate removal of dead tissue or bone, and repeating the surgery or approaching through another area may be indicated.

Splinting or immobilization postoperatively is not done, except in the rare cases that may have unusual pain until packing is removed. No attempt to obtain fusion in peripheral joints is made, and the patient is encouraged in active motion from the beginning. In weight bearing joints, weight bearing, first with crutches, is allowed as tolerated by the patient. General supportive measures to improve nutrition and anemia are carried out, and the patient is maintained on streptomycin, para-aminosalicylic acid and isonicotinic acid hydrazide combinations until long after the sinus is closed. In the early series, a plan of maintenance on streptomycin for 50 per cent of the time beyond that required for complete closure of the sinus was followed. In more recent years, the patient has been taken off streptomycin and placed on isonicotinic acid hydrazide and maintained for a year or more, despite closure and x-ray evidence of healing.

An analysis of the 194 operations performed lead to this general conclusion:

1. Following adequate surgical drainage and drug therapy, destruction has been found to cease. Serial x-ray films and follow-up of cases for up

to 10 years reveals progressive healing, and no reactivation of the bone lesions to occur, clinically, symptomatically or by x-ray study.

2. The operated lesion will heal and remain healed, although other lesions have been known to develop or progress, even during the period of streptomycin and isonicotinic acid hydrazide administration.

3. A good functional range of painless motion has been attained in peripheral joints, and in the few cases where arthrodesis was required, fusion occurred rapidly.

4. Secondary infection has not been a problem.

Our patients ranged from 11 months to 79 years of age. Of the 142 treated, only 10 are known to have died, and of these only one death is related to the surgery performed, occurring in an elderly woman with dorsal spine involvement and partial paraplegia, who fell out of bed at night three days postoperatively, sustaining a severe laceration of the scalp and dying suddenly the next morning.

Five died from seven to 42 months following surgery of bone lesions, but death was due to far advanced pulmonary tuberculosis and the bone lesions were apparently healed.

Two died from metastatic carcinoma, one from an automobile accident and one in the electric chair, convicted of murder.

Of the 142 patients, 52 had active concommitant pulmonary tuberculosis, and these represent an analytical study of particular interest to this group. If we divide these 52 cases into two five year periods, there is this occurrence: 28 between September, 1946 and September, 1951 and 24 between October, 1951 and the present. The comparative incidence of concurrent osseous lesions is thus found to be essentially the same, with no tendency for its presence to be lessened by our changed therapeutic regimen of the past 10 years.

Although accurate figures are not obtainable for comparison, it is our definite impression that this incidence of bone lesions was not found or treated prior to the onset of this study. The explanation probably lies in a few factors:

1. Careful attention to complaints of patients referable to the musculoskeletal system, with orthopedic and x-ray examinations done routinely. Many early lesions were diagnosed which we feel would otherwise be missed.

2. Increased recovery rate and longevity of the patient with pulmonary lesions has allowed for the higher percentage of rate of diagnosis of bone lesions, particularly since bone lesions are known to progress if unoperated, despite drug administration.

Effect of Treatment

The presence of even far advanced pulmonary tuberculosis and poor general condition of the patient has not interfered with surgical attack of active bone lesions. Both lesions are actively treated concurrently, and in general one can expect a definite improvement in the patient's condition to occur, as evidenced by weight gain, increased feeling of well being and more rapid

clearing of the pulmonary lesion as evidenced by x-ray, negative sputums, etc. Although this does not always occur, the improved condition has often resulted so rapidly as to be beyond the realm of coincidence.

This approach to the problem of the osseous lesion has coincided well with the tendency to treating the pulmonary lesion in a more ambulatory manner with lessened hospitalization.

RESUMEN

Una teoría radicalmente opuesta a las otras en el tratamiento de las lesiones óseas se ha presentado. Habiéndose llevado a cabo el tratamiento de acuerdo con ella en 194 lesiones generalmente no seleccionadas en cuanto a la edad de los enfermos, ubicación en el cuerpo, estado de evolución de la lesión ósea o pulmonar o las condiciones generales. Los enfermos se han seguido observando hasta por 10 años y no presentan tendencia a la recurrencia, falla de la curación o progreso de la destrucción ósea por la infección.

Los enfermos con lesiones pulmonares se han beneficiado grandemente en general por este tratamiento radical de la lesión ósea según lo demuestran la limpieza de la afección pulmonar, la mejoría del estado general y el decrecimiento de la mortalidad.

RESUME

L'auteur présente une théorie radicalement opposée aux idées en cours sur le traitement des lésions osseuses. Elle a été appliquée dans 194 cas, généralement sans tenir compte ni de l'âge du malade, ni de la localisation, ni du stade de la lésion osseuse ou des altérations pulmonaires, ni de l'état général du malade. Les malades ont été suivis pendant plus de 10 ans, et ne présentent aucune tendance à la rechute, à l'arrêt de la guérison, ou à la progression de la destruction osseuse par l'infection.

Les malades atteints de lésions pulmonaires ont tiré en général un grand bénéfice de ce traitement radical de la lésion osseuse, mis en évidence par le nettoyage plus rapide de l'état pulmonaire, l'amélioration du bien-être général, et la décroissance de la mortalité.

ZUSAMMENFASSUNG

Bericht über eine radikal oppositionelle Theorie der Behandlung von Knochenherden, die an 194 Herden ausgeführt wurden, die meistens nicht ausgewählt waren hinsichtlich Alter des Patienten, Lokalisation im Körper, Stadium der Ausbreitung des Knochen- oder Lungen-Herdes, oder des Allgemeinzustandes des Patienten. Die Patienten wurden bis zu 10 Jahren nachuntersucht und boten keine Tendenz zum Rückfall, Zerstörung des Heilungsprozesses oder zum Fortschreiten der Zerstörung des Knochen infolge Infektion.

Patienten mit pulmonalen Herden haben im Allgemeinen erheblichen Nutzen gezogen aus dieser radikalen Behandlung des Knochenherdes, wie sich an der rascheren Rückbildung der pulmonalen Veränderungen, der Besserung im Allgemeinbefinden und der Abnahme der Mortalität zeigte.

Varicella Pneumonia*

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Varicella is usually a rather benign disease in children that occasionally occurs in adults. It is infrequently complicated by secondary invasion of staphylococci and streptococci, but these complications are not considered serious except in debilitated persons. There have been reports recently in the literature indicating that the virus of chickenpox can involve the lungs and may have a grave prognosis when it does.

In 1934 Cowdry[1] studied, described, and called attention to the intranuclear inclusions considered to be pathognomonic in viral infections. The seriousness of the involvement of tissues, other than the skin and adjacent mucous membranes, was apparently not considered until Johnson,[2] in 1940, reported intranuclear inclusion bodies in the organs of a seven-month-old male child who died with chickenpox; however, in this case the lungs were not involved.

It was not until 1942 that Waring, Neuberger, and Geever[3] first reported two cases of typical chickenpox pneumonia. One of their cases, a 33-year-old white man, recovered, but the other, a 40-year-old white man, died in four days. At autopsy diffuse pneumonia was noted that was attributed to the virus of chickenpox. In 1943 Rausch, Grable, and Musser[4] reported atypical pneumonia in a 27-year-old white man who had Varicella. He recovered. In 1947, Grayson and Bradley[5] reported a 34-year-old white man with disseminated chickenpox, involving the lungs and kidneys, who was well in 30 days. He was treated with sulfadiazine. Also in 1947, Claudy[6] described a case of Varicella pneumonia in a 32-year-old white woman who died in eight days. Frank[7] and Eisenbud[8] each recorded deaths in 1950; the first, a 34-year-old white woman, who was ill six days; the other was A 71-year-old white woman. In 1951 Michel, Coleman and Kirby[9] reported the case of a 27-year-old white man who recovered in eight days. He was treated with chlortetracycline. Also, recoveries were reported of three cases by Saslaw, Prior, and Wiseman[10] in 1953; a 28-year-old white woman and two white men, one 38 and one 42 years of age. The first and third cases were treated with penicillin, the second with chlortetracycline.

Thus, of the 11 cases of varicella pneumonia found in the literature, seven recovered and four died. In view of its serious prognosis and the fact that so few cases have been recorded, it was thought that the report of a death from Varicella pneumonia, occurring in Riverside Hospital this year, should be added to the scant literature.

Case 1: M. G., a 27-year-old white housewife was admitted to the hospital December 11, 1955. She was six months pregnant. She complained of chest pain, a persistent cough and shortness of breath. Her illness had begun three days previously with the development of fever and typical chickenpox eruption. The day after she became ill the vesicles spread over her face, trunk and thighs, but she felt better generally.

*Presented to the Riverside Hospital staff meeting, March 23, 1956.

The next day she developed persistent intractable cough, with feeling of breathlessness, which became progressively worse. The sputum was scant, white and frothy. On the day of admission, shortness of breath and cough were distressing, and the sputum had become blood-tinged. The fever had been and was moderate throughout the entire illness.

The past history was non-contributory. She had never had chickenpox, but her two children were recovering uneventfully from the disease. Her previous and present pregnancies had been normal.

On examination she appeared acutely ill, was coughing frequently and raising small amounts of frothy, blood-tinged sputum. The rectal temperature was 100.4° F. and the pulse 128. She was cooperative but dull in her reactions. There were typical vesicles over the face, head, oral mucosa, trunk, and thighs. The lesions were of various ages but pyoderma was not evident. There was slight cyanosis of the lips and nail beds. There was impaired resonance at the right base with fine and medium moist rales. Rales at the left base, posteriorly, were also present. The heart was negative except for tachycardia. The abdomen was distended and tympanitic. The reflexes were normal.

The clinical diagnosis was varicella with pneumonia, right lower lobe, probably spreading.

The blood showed 4.1 million red cells per cmm.; 13.6 grams hemoglobin; and 8,850 white cells per cmm. with 14 per cent nonsegmented neutrophils, 76 per cent segmented neutrophils, and 10 per cent lymphocytes. Urinalysis was negative except for specific gravity of 1.003.

She was placed in an oxygen tent, started on penicillin intramuscularly and erythromycin orally. She was given 10 per cent glucose in Ringer's 1000 cc. intravenously at a slow rate, and sedation as needed. A transfusion of whole blood was advised but not completed.

Her course in the hospital was rapidly downhill, and she expired 18 hours after admission, four days from the onset of illness.

Autopsy protocol by Dr. C. L. Sinclair, excluding the head, listed the following findings:

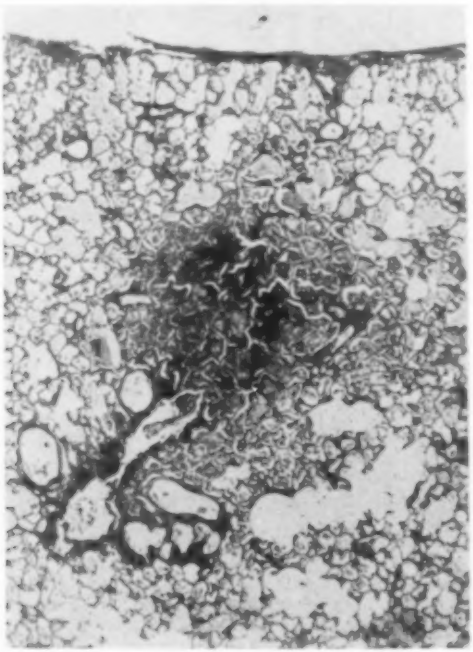

FIGURE 1: (M. G.) Section of lung showing a focus of hemorrhagic necrosis and consolidation, 30x.

"The breasts are slightly enlarged and are fairly tense. The abdomen is moderately enlarged and the uterus is readily felt to a level approximately two inches above the umbilicus. Scattered over the skin surface, particularly about the face, neck, back, chest and trunk down to approximately level with the symphysis pubis, are numerous crusting skin lesions. Intermingled among these lesions are a fair number of reddish vesicular lesions.

"A small amount of clear, serous fluid is noted in either pleural cavity and the pericardial sac.

"The right lung weighs 1,280 grams and the left 1,150 grams. The pleural surfaces of both lungs are faintly mottled, dark-grayish-purple in color. The bronchi throughout all portions of both lungs are filled with a thin, slightly frothy, slightly turbid, yellowish-red fluid. Cut surfaces of all portions of the parenchyma show essentially similar changes. The lung parenchyma is moderately firm and homogeneous, dark-grayish-purple. No crepitation is noted and the cut surfaces exude small amounts of thin serosanguinous fluid.

"The spleen weighs 265 grams. It has a slightly tense, smooth, grayish-purple capsule. The cut surfaces of the spleen bulge slightly above the level of the cuts made, and the splenic parenchyma is moderately friable, and is dusky-purplish-red in color.

"The uterus is symmetrically enlarged, and readily palpable through the uterine wall are fetal parts. On opening the uterus, it contains a male fetus weighing 1,550 grams. No external abnormalities are noted on examination of the fetus.

"*Microscopic:* Sections from all lobes of both lungs show essentially similar changes. All alveoli are filled with fluid and/or fibrin. Throughout this material, scattered macrophages laden with yellowish pigment are noted. The alveoli also contain an occasional lymphocyte and macrophage. The alveolar walls are moderately edematous, and in the nuclei of the stromal cells an occasional intranuclear inclusion body is recognized. Scattered throughout the section an occasional alveolus is noted which is lined by a fairly thick hyaline-like membrane. Throughout the lung sections occasional small areas of necrosis are noted which are moderately infiltrated by neutrophils. Many of these small areas of necrosis appear situated adjacent to bronchioles, Figure 1.

"Sections of the liver show normal lobular pattern with good preservation of the hepatic cells. In some portal areas there is a diffuse and moderate lymphocyte infiltration, but no increase in fibrous tissue.

"The sinusoids of the spleen are fairly distinct and contain only small amounts of blood. The germinal follicles are well defined and do not contain germinal centers. A mild reticuloendothelial hyperplasia is noted throughout the splenic pulp.

"An occasional glomerulus shows partial fibrosis but otherwise no significant histological changes are noted in the kidney sections.

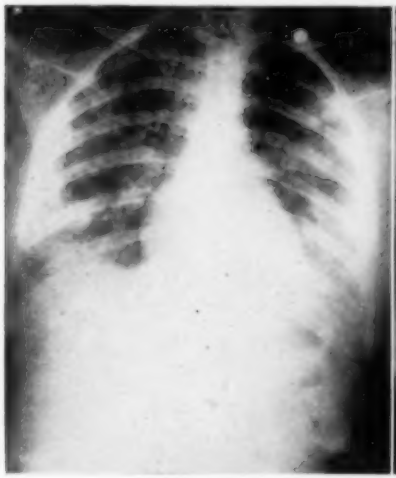

FIGURE 2

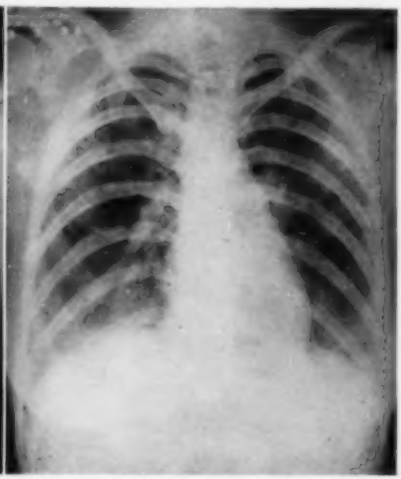

FIGURE 3

Figure 2: (E. B.) Chest film taken March 3, 1956, three days after onset of disease.—*Figure 3:* (E. B.) Chest film taken March 7, 1956, as a follow-up.

"Section of skin shows an intraepithelial vesicle. The epithelial covering of the vesicle is only approximately one cell thick. The vesicle contains degenerated epithelial cells tending to occur in clusters. Many of these cells show fairly large intranuclear amphophilic inclusions with a clear zone about the inclusion. The chromatin of these nuclei is clumped about the nuclear membrane. The base of the vesicle shows a diffuse infiltration of lymphocytes, plasma cells and a few neutrophils. The epithelial lining of the base apparently has been completely destroyed.

"*Anatomical Diagnosis:* 1. Varicella pneumonitis, extensive, all lobes, Lipschutz intranuclear inclusion bodies in the septal cells were demonstrated. 2. Varicella. 3. Pregnancy, six months."

Case 2: E. B., a 26-year-old white housewife was first seen at home February 29, 1956. She had generalized skin eruption, fever, toxicity and general malaise. She had never had chickenpox, but two of her children were recovering from the disease. Because of the severity and extent of the eruption she had been started on tetracycline two days previously. At the time of the first visit prednisone, 25 mg. daily, was added. The following day she was worse, with oral temperature of 104 degrees F., dyspnea, tachypnea and moderate apprehension. The lungs were negative to physical examination. The buccal cavity was extensively involved with varicella lesions. Two days later she was seen again, at which time her condition seemed critical and she was admitted to the hospital March 2, 1956. She was acutely ill, dyspneic, apprehensive, with a pulse of 120 and respirations of 30. The temperature was 102.4 F., rose to 103.6 F. but fell to normal by lysis during the next two days.

Physical examination showed the typical lesions of varicella covering the skin of the entire body, including the mouth, pharynx and vagina. There were medium moist rales at both bases but no sign of frank consolidation.

A bedside x-ray film of the lungs the day after admission showed a diffuse, patchy infiltration throughout both lung fields, interpreted as consistent with extensive bronchopneumonia, Figure 2. Five days later a chest x-ray film showed considerable clearing, Figure 3. The blood count on admission revealed hemoglobin of 15.3 grams; hematocrit of 49; white blood cells 6,950 per ccm., with 56 per cent segmented neutrophils and 44 per cent lymphocytes. Urinalysis was negative. A repeat blood count on March 2 showed essentially the same findings.

The treatment comprised tetracycline given primarily to prevent secondary pyoderma; benadryl to control pruritus; sedation as needed; oxygen by tent; and penicillin with streptomycin. No additional steroids were given. Chlorpromazine was added the day after hospitalization because of marked restlessness and apprehension. On the night

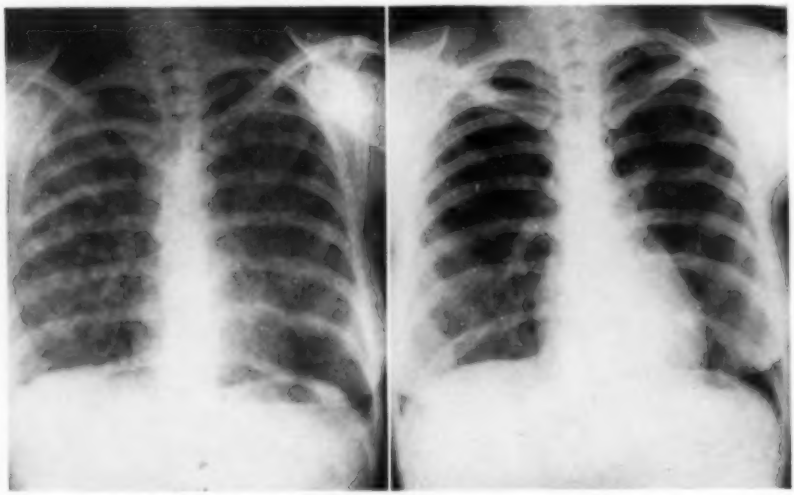

FIGURE 4 FIGURE 5

Figure 4: (M .C.) Chest film taken August 25, 1954, five days after the onset of illness. —*Figure 5:* (M. C.) Chest film taken September 28, 1954, as a follow-up.

of admission 20.0 cc. of Gamma globulin was given intramuscularly at a single sitting. Two days after this there was definite improvement in every respect. The temperature, pulse and respiration subsided proportionately. By March 8, six days after admission, she was feeling quite well. The skin lesions were beginning to show signs of involution. Examination of the lungs was negative. By March 12, the day of discharge, she felt quite well, was up and about, and the skin was clearing rapidly.

Case 3: M. C., a 21-year-old white housewife was admitted to the hospital August 24, 1954. She had had a typical chickenpox rash for four days, and her son was convalescing from this disease. Two days before admission she developed chills, fever and headaches, followed by non-productive, harrassing cough.

She was six months pregnant.

On admission the oral temperature was 102 F., the pulse 104 and the respirations 23. She appeared acutely ill and toxic. Except for the typical varicella rash covering her entire body and face, the physical examination was negative.

The hemoglobin was 11.6 grams. The white blood cell count was 17,000 per cmm. with 89 per cent neutrophils and 11 per cent lymphocytes. Blood serology was negative, also urinalysis was negative.

A chest x-ray film the day after admission showed a diffuse "bronchopneumonic process," Figure 4. She was given oxytetracycline for seven days. Her temperature and pulse became normal in six days, and she was discharged from the hospital eight days after admission. A follow up chest x-ray film was negative, Figure 5.

Comment

Three cases of severe varicella pneumonia have been described. The first case went downhill rapidly and expired in four days, 18 hours after hospitalization.

The second appeared equally ill and toxic, except for cyanosis, but she recovered in 10 days. Because of the experience with the first case and the fact that viral instead of bacterial pneumonia was suspected, Gamma globulin was used in the hope that antibodies (antiviral) in this material would be effective. There has been no proof that the sulfa drugs or antibiotics are effective in the treatment of purely viral disease. However, it is not thought that this one case proved that the use of Gamma globulin altered the course specifically, but this material certainly has a rational basis for treatment in other viral diseases. It is suggested that Gamma globulin be tried in other cases of Varicella pneumonia.

The third case was obtained from Dr. Quentin Legg, radiologist at the Riverside Hospital, who secured permission to report it from the Langley Field Air Force Base Hospital. This patient recovered in eight days on treatment with oxytetracycline.

SUMMARY

Three cases of severe varicella with pneumonia or pneumonitis have been presented. One expired and the etiology was proved at autopsy. The other cases recovered uneventfully. Case 2 was not only given antimicrobial drugs, but also Gamma globulin. Case 3 received oxytetracycline.

RESUMEN

Se presentan tres casos de varicela con neumonía o neumonitis. Uno de ellos falleció ya la etiología se comprobó a la autopsia. Los otros dos casos se recuperaron sin complicaciones. En el caso 2 no sólo se le dieron drogas antimicrobianas sino también Gamma globulina. En el caso 3 se usó oxitetraciclina.

RESUME

L'auteur présente trois malades atteints de varicelle sévère avec pneumopathie associée. L'un mourut et l'étiologie fut démontrée à l'autopsie. Les autres guérirent sans complication. Le deuxième cas fut traité non seulement par des médications antimicrobiennes mais encore par la gamma-globuline. Le troisème cas fut traité par l'oxytétracycline.

ZUSAMMENFASSUNG

Es werden 3 Fällen schwerer Varizellen mit Pneumonie oder Pneumonitis vorgestellt. Einer verstarb und die Aethiologie wurde bei der Sektion bestätigt. Der andere genas ohne Besonderheiten. Fall 2 erhielt nicht nur antimikrobielle Heilmittel, sondern auch Gamma globulin. Fall 3 erhielt Oxytetracyclin.

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INFLUENZA

From the Council on Public Health, American College of Chest Physicians

Influenza epidemics in the Orient, which have been reported in the press during the past few weeks, are being watched with concern by public health authorities in the United States and in other parts of the world. The first outbreak reported was in Hong Kong, and it was followed by others in Singapore, Formosa, the Philippine Islands, and other countries in the Far East, as well as in American military personnel stationed there and on ships returning to the United States.

The illness reported has in most cases been mild, characterized by fever, malaise, headache, mild respiratory symptoms, and a dry cough. Usual duration has been 2 or 3 days, few complications have been reported, and case fatality has been low. Attack rates, however, have been high—in some areas, as high as 50 per cent of certain population groups have been affected.

Isolates from these epidemics have been examined at the Walter Reed Army Institute of Medical Research, the Public Health Service Communicable Disease Center Virus Laboratory at Montgomery, Alabama, and at other laboratories in the United States. Virus strains were found to be similar to each other but quite different from prototypes isolated from outbreaks in the past. Complement fixation tests demonstrated that the strains were type A influenza virus, but antibody in human and animal antisera prepared against other type A strains did not inhibit hemagglutination by the new variants. No antibody has been demonstrated in sera from people residing in the United States. These strains represent a new set of antigenic variants which could circulate readily throughout the world. On the basis of these findings, the World Health Organization has alerted all influenza centers, and new strains have been distributed for further intensive studies.

Experience in the Far East indicates that influenza vaccines in current use do not protect against the new strain. Prototype virus has been submitted to several United States biologics companies, and they are preparing to manufacture vaccine which will probably be available in the fall.

In view of the extent and rapidity of travel between the United States and the Far East, this newly recognized strain of influenza will probably be introduced into this country. Our history of influenza, however, is such that outbreaks of any proportion are unlikely to occur during the summer months. There may be scattered groups of cases, traceable to individuals recently returned from the Far East.

The Public Health Service has taken steps to study and to help control any local outbreak that may occur. Health departments of all the States have already been informed about the situation. The Division of Biologics Standards of the National Institutes of Health is working with the pharmaceutical industry in expediting the production of vaccine. The Virus and Rickettsia Section of the Communicable Disease Center Laboratory

(which is the WHO Influenza Center for the Americas) is preparing diagnostic reagents for the recently isolated strains and distributing them to regional and collaborating laboratories throughout the country and the Western Hemisphere. Studies are being carried on at this laboratory of all recently isolated strains of influenza obtained through the WHO. The National Office of Vital Statistics is keeping public health authorities informed about developments. The Division of Foreign Quarantine is informing persons arriving from affected areas that should they become ill they should see their physicians without delay. The Epidemic Intelligence Service of the Communicable Disease Center, with officers assigned throughout the country, is ready to assist State and local health departments in the investigation of any occurrence of influenza.

The key to the situation, of course, is in the hands of the practicing physician. His alertness to any cases of influenza-type illness among his patients—or of this kind of illness in persons recently returned from the Far East, or their families or associates—will provide the information needed to deal with the problem before it becomes widespread. It is urgent that such information be given promptly to local health authorities, to protect the community and the country from the possibility of a full-scale epidemic.

Because of their special competence in respiratory disease, Fellows of the American College of Chest Physicians have a definite role to play in the surveillance and control of influenza. They will undoubtedly consider a diagnosis of influenza in any patient with symptoms of upper respiratory disease. The definitive diagnosis can be made only through virus isolations in the acute phase or by comparative titers of serum from the patient when he is acutely ill and when he is convalescent. Virus isolations require nose and throat washings obtained preferably during the first 3 days of illness and while the patient is still febrile, although virus may be recovered as long as 7 days after onset. The patient should gargle 3 times using about 15 ml. of diluent (broth, skimmed milk or distilled water) and returning the washing each time to the paper cup. Some infective material may be brought from the trachea into the pharynx if the patient will cough. The washings should be transferred to a closed tube for transportation to the laboratory and tested as soon as possible. If a delay of more than a few hours is necessary, the fluid should be kept chilled at refrigerator temperatures. When longer periods of storage are unavoidable, the washing should be frozen and stored, preferably near —70 degrees C. Serum samples should also be taken, one during the time of illness and a second 2 to 4 weeks later.

Not all laboratories are prepared to do virus isolation and serology for influenza. State health departments, however, can either do these procedures or refer the specimens to influenza reference laboratories such as the one at the Public Health Service Communicable Disease Center Virus and Rickettsia Laboratory, Montgomery, Alabama.

Although individual cases of influenza are not required to be reported by a physician, in order that the first signs of an outbreak can be detected,

physicians should call health officers about suspected and proven cases of influenza occurring this summer and fall.

Fellows of the College can also be especially effective in this situation by calling it to the attention of other physicians in their community, advising on diagnosis and treatment, and stressing the importance of recognizing and treating complications.

In countries not as yet affected by the current influenza epidemic, Fellows of the College should be on the alert for symptoms of the disease and take measures to detect the disease and prevent its spread.

Robert J. Anderson, Atlanta, Georgia, Chairman
Irving Willner, Newark, New Jersey, Vice-Chairman
Clifton F. Hall, Springfield, Illinois, Secretary
Frederick B. Champlin, Richmond, Virginia
Joseph S. Hiatt, McCain, North Carolina
Philip H. Narodick, Seattle, Washington
Ethan B. Pfefferkorn, Oshkosh, Wisconsin
Arnold B. Rilance, New Haven, Connecticut
Leo V. Schneider, Bethesda, Maryland

CURRENT STATUS OF THE NEW MEXICO FIELD TUBERCULOSIS STUDY PROGRAM

FROM THE COMMITTEE ON INDIAN AFFAIRS, AMERICAN COLLEGE OF CHEST PHYSICIANS

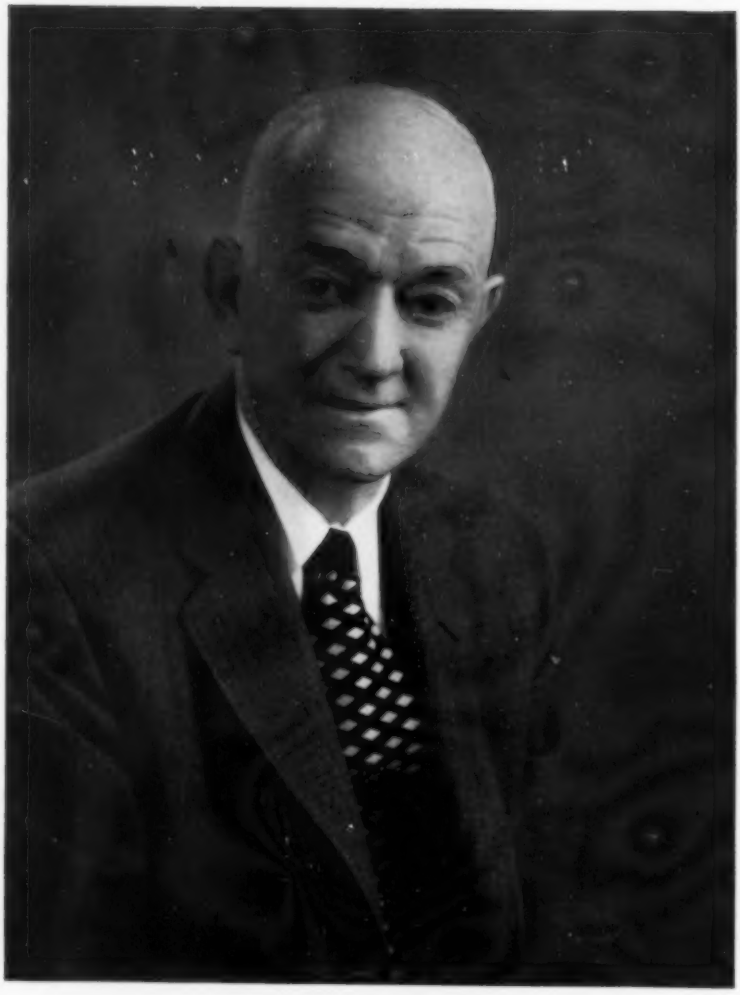
To date the parents of 5,091 Indian children ranging in age from three months to 15 years of age, in the States of New Mexico and Colorado, have signed requests to have their children participate in this study to determine the value of the daily administration of isoniazid, in doses of approximately 10 milligrams per kilogram of body weight, in the care and/or prevention of tuberculosis in childhood.

All children are tested with a single introdermally administered dose of 5 tuberculin units. The tests are read after an interval of 72 hours and the results are recorded in terms of millimeters of induration. It was found that 11.1 percent reacted with an induration of 6 millimeters or more. Approximately fifty percent of the children are selected as controls by randomization of villages. However, any child found to be a recent converter is removed from the program and placed on treatment in the home, clinic, or hospital with isoniazid immediately after a chest x-ray has been obtained. All children are routinely examined with chest x-ray once a year. No untoward results have been discovered.

Because of previous efforts at tuberculosis control in this area the number of reactors under observation may not be sufficient for adequate evaluation. Plans are being considered for the inclusion at a later date of new areas where the incidence of infection is believed to be higher.

The Division of Indian Health of the Public Health Service is anxious to ascertain factual knowledge as soon as practicable and is appreciative of the efforts of the College in the promotion and development of the program.

Arthur W. Dahlstrom, Albuquerque, New Mexico, Chairman
Carl H. Gellenthien, Valmora, New Mexico, Vice-Chairman
William R. Hewett, Tucson, Arizona, Secretary
James J. Barfield, Fort Stanton, New Mexico
Roy F. Goddard, Albuquerque, New Mexico
J. E. J. Harris, Albuquerque, New Mexico
Edward W. Hayes Sr., Monrovia, California
Francis M. Pottenger Sr., Monrovia, California



William Hugh Feldman

DR. WILLIAM H. FELDMAN
RECIPIENT OF 1957 COLLEGE MEDAL*

Dr. William Hugh Feldman was born in Scotland on November 30, 1892 and migrated to the United States with his mother at the age of two. They settled in Paonia, a small town in Western Colorado, where Dr. Feldman received his grade school and high school education. He enrolled at the Colorado State College at Fort Collins (now known as Colorado State University) and received his D.V.M. Degree in 1917. That summer he joined the faculty of the Veterinary Division of Colorado State College, teaching laboratory classes in pathology and bacteriology, as well as meat inspection and pharmacology.

In 1920 Dr. Feldman went to Ann Arbor, Michigan to take Dr. A. S. Warthin's course in pathology. This experience was so stimulating and inspiring to him that he became thoroughly inoculated with the desire to explore at least a few of the countless facets of pathology. In 1927, the late Dr. Ralph G. Mills, formerly Professor of Pathology at the Medical School of the University of Colorado, suggested Dr. Feldman's name to fill the position as veterinary research pathologist at the Institute of Experimental Medicine, Mayo Clinic and Mayo Foundation; he joined the staff in June, 1927 as Associate in the Division of Experimental Medicine and Instructor in comparative pathology, Mayo Foundation, Graduate School of the University of Minnesota.

Dr. Feldman received his M.S. Degree in Colorado in 1926, using as material for his thesis neoplasms of animals. He expanded this study after he arrived in Rochester and, as a consequence, his first book "Neoplastic Diseases of Domesticated Animals" was published in 1932 (now out of print). Dr. Feldman then transferred his interest and energies to the laboratory and experimental aspects of tuberculosis, and having found that there did not exist a comprehensive monographic account of avian tuberculosis infections, he launched an extensive investigation of this disease. His book "Avian Tuberculosis Infections" was published in 1938 by Williams and Wilkins. Upon the completion of this study, Dr. Feldman's laboratory continued in the field of tuberculosis and other myobacterial infections and at the suggestion of Dr. H. Corwin Hinshaw, work was begun on the chemotherapy of experimental tuberculosis.

Since 1944, Dr. Feldman has been Professor of Comparative Pathology, Graduate School, University of Minnesota (Mayo Foundation). He is the author of over 300 contributions to scientific periodicals; he delivered the John W. Bell Lecture on Tuberculosis in 1942, the Harben Lectures on "The Chemotherapy of Tuberculosis—Including the Use of Streptomycin" in London, 1946, and the Alvarenga Prize Lecture, Philadelphia in 1946. At the invitation of the Medical Research Council of Ireland, he participated in the Colloquium on the Chemotherapy of Tuberculosis held in Dublin, 1951. In 1953 he was appointed a member of the Governor's Commission for the Study of the Tuberculosis Facilities in the State of Minnesota.

Dr. Feldman is a member of the Minnesota Pathological Society, Minnesota State Medical Association, American Association of Pathologists and Bacteriologists, American Trudeau Society, American and Minnesota Veterinary Medical Association; American Society of Experimental Pathology and the American College of Veterinary Pathologists, and has held many important offices in these societies.

Photography is Dr. Feldman's hobby. He has always believed in the importance of technically good photographic illustrations to supplement the text of technical reports. He has, therefore, developed the knowledge and skills necessary to make technically good pictures of both gross and microscopic materials. Thus, Dr. Feldman has found in his research work that the photography done in relation to observations in the laboratory has been fun and relaxation. During the past several years, Dr. Feldman has extended his hobby to doing camera portraits of men in science, medicine and music.

Dr. Feldman resides in Rochester, Minnesota with his wife, Ruth Harrison Feldman; they have a daughter, Mrs. John F. Connelly Jr., and a son, William.

*Presented by Dr. H. Corwin Hinshaw at the Presidents' Banquet, 23rd Annual Meeting, American College of Chest Physicians, New York City, June 1, 1957.

Burgess Lee Gordon, M.D.
President
American College of Chest Physicians, 1957-1958

DR. BURGESS L. GORDON
TAKES OFFICE AS COLLEGE PRESIDENT

Dr. Gordon was born in Spokane, Washington, April 10, 1892. He received the degree of Bachelor of Arts and the honorary degree of LL.D. from Gonzaga University, and in 1919 the degree of Doctor of Medicine from the Jefferson Medical College. His internship was served at the Jefferson Hospital in Philadelphia. In 1921 he was appointed resident physician of the Peter Bent Brigham Hospital, Boston, where he remained until 1926. During this association he also served as teaching fellow in medicine of the Harvard Medical School. On returning to Philadelphia he began a series of associations leading to the appointment of Assistant Professor of Medicine and Director of the Department for Diseases of the Chest, Jefferson Medical College and Hospital; Physician to the Pennsylvania Hospital; and member of the Board of Directors and Visiting Physician to the White Haven Sanatorium. He was elected in 1937 to the Board of Managers of the Mercy-Douglass Hospital.

His military services began in 1922 as Chief of Medicine of the Harvard Unit. In 1942 he became successively Chief of Medicine, 38th General Hospital, serving in Texas and Cairo, Egypt; Chief of the Medical Service and Executive Officer, 21st Station Hospital stationed in Tel-Aviv, Israel, Baghdad, Iraq and Khoramsharrh, Iran; Commanding Officer of the 30th Station Hospital in Teheran, Iran, and Panagarrah, India; and Commanding Officer, 263d General Hospital, Calcutta, India. On returning to the United States he was appointed to the Hospital Division of the Surgeon General's Office and later served as Chief of Medicine, U. S. Army General Hospital, Camp Picket, Virginia. He retired from active service with the rank of Colonel, to be appointed Consultant to the Surgeon General for the period 1947-51. He returned to the Jefferson Medical College as Associate Professor of Medicine and became Director and Physician-in-Chief of the Barton Memorial and White Haven Divisions of the Jefferson Hospital; he was promoted to Clinical Professor in 1948.

He resigned from his positions at the Jefferson Medical College and Hospital in 1951 to become President and William J. Mullen Professor of Medicine of The Woman's Medical College of Pennsylvania. In addition to being President-Elect of the American College of Chest Physicians, he is Secretary of the Section on Diseases of the Chest of the Americal Medical Association.

The new President of the College has long been interested in the fields of internal medicine with special reference to clinical cardiopulmonary physiology and the development of apparatus for the investigation and treatment of disturbed conditions of the chest. He studied the effects of marathon running on the heart, lungs and blood conditions in the Boston races of 1923-24-25 and in 1928 observed runners during the transcontinental foot race. In 1948 he became director of studies in silicosis sponsored by the Anthracite Health and Welfare Fund of the Jefferson Hospital. His publications in medical journals and textbooks total more than 200. He is associate editor of the Oxford Loose-Leaf Medicine; editor of Diseases of the Chest, Practitioners Series of the Oxford Press; and editor of Clinical Cardiopulmonary Physiology, sponsored by the American College of Chest Physicians. He has served in various capacities as a member of the Philadelphia County Medical Society; the Council, College of Physicians; the Philadelphia Tuberculosis and Health Association; Advisory Committee of the Health and Welfare Council and the Visiting Nurse Society.

Dr. Gordon and his wife, Margaret, reside in Philadelphia, Pennsylvania. They have one son, Burgess. Dr. Gordon's mother and brothers, Ralph and Charles, live in California.

President's Address

It is a privilege this evening to welcome you, the new Fellows of the College. We have been looking forward to this occasion with great interest and pleasure. It is stimulating to have in our midst new associates whose wide experience will enrich our thinking and discussions.

Today we are facing the most important and challenging period of our history. In a very real sense a stirring evolution is upon us. The specific infections, once the dreaded spector of untimely death and hardship, are giving way to a veritable avalanche of degenerative conditions. And thus we may well pause to wonder if our gains for total health are real or delusionary. There is much food for thought: Are we approaching an era when physiologic disability, especially in our aging population, will become a more significant problem than infection *per se?* Is the time at hand when the chest physician must focus attention on the basic mechanisms rather than the stereotyped classifications of signs and symptoms? Are the antibiotic drugs, as we now know them, only the forerunner of even more specific agents? Should we look to chemotherapy rather than surgery and roentgenotherapy for important headway against cancer? Have we solved the tuberculosis problem? Are we closing sanatoria prematurely? Will surgery tend to become more and more the artful procedure for reconstruction, less and less the extirpator of diseased tissue? These and other questions are commanding increasingly the attention of the chest specialist.

You, the new Fellows of the College, have a tremendous opportunity to explore the unbeaten paths of chest medicine. Your practice and clinics are rich depositories of knowledge, waiting only to be screened and ferreted. This college was founded with the sole purpose of providing opportunities for the exchange of experience and ideas between physicians—a medium open to men and women like you with an insatiable thirst for knowledge. You were carefully selected because of your past contributions and great promise in some particular field of chest medicine. Do not hide your light under a bushel basket. Take every opportunity to use the College and its chapters as your forum. We welcome your presentations and look forward to your articles in our journal, pamphlets and textbooks.

To ride the crest of this momentous transition in thoracic medicine the College calls to one and all for active participation. In order that each one of you may find his own niche in the College circle, may I suggest that you carefully read the list of committees and become acquainted with their respective chairmen. Select some area that would be interesting and useful both to the College and to you, personally. It may be in the fields of undergraduate or postgraduate medical education, industrial medicine, tuberculosis or cardiopulmonary physiology. Start at the grass roots in your local or state chapter and progress to national and international levels. In so doing you will make warm and valuable friends—all dedicated to the furtherance of our specialty.

In this atomic age of medicine, when science is in the saddle, the American College of Chest Physicians cannot afford to remain static nor falter in its course. Imagination and resiliency, both in policy and program, are vital. For some faulty deviation could neutralize even the most constructive effort. To over-play fundamental medicine when clinical aspects require elucidation would be to classify the society as one for investigators only. Diversification provides the most logical course. It is interesting that the College long has recognized the trends most acutely, first in providing two types of programs running simultaneously—one clinical, the other fundamental—one cardiac, the other pulmonary—with addresses and panels interspersed in order to bring into clear perspective data that would correlate and emphasize. The fireside conferences, with the membership under the guidance of discussion leaders, provide a proving ground for ideas and subject matter that may be introduced in formal presentations at a later date. This activity brings the members together in friendly and spirited discussion.

As you turn homeward-bound please resolve to consider ways and means to keep our college compliant with the trends of modern medicine. Please keep

this thought ever to the fore: We want a college composed of members who are able to contribute something real to our stock of knowledge. If there is some phase of the meeting that could be amplified, consult with the chairman of the scientific program committee so that new material may be considered for the next year. And may I also suggest that you remain in touch with the home office, your regent, your governor and the officials of your local chapter. It will be through these avenues of professional interest and fellowship that you and the College will press forward to even greater heights.

In closing, may I predict that you are about to begin one of the most satisfying associations of your medical life.

Burgess L. Gordon

Presented at the Convocation, 23rd Annual Meeting, American College of Chest Physicians, New York City, June 1, 1957.

23rd ANNUAL MEETING

The largest annual meeting in the history of the American College of Chest Physicians was held in New York City, May 29 through June 2, at the Hotel Commodore. Registration for the meeting reached a total of 1884, representing 1051 members of the College, 448 non-member physicians, 263 ladies and 122 exhibitors. Twenty-seven technical exhibits, officially opened at a ribbon-cutting ceremony on Wednesday, May 29, were on display throughout the meeting.

On Saturday, June 1, Fellowship Certificates were awarded to 217 physicians at the Annual Convocation of the College. An Honorary Fellowship in the College was conferred upon Dr. Ethan Flagg Butler, Elmira, New York, a pioneer in thoracic surgery in the United States. In a special ceremony during the Convocation, the Panamanian and Nicaraguan Chapters presented their national flags to the College for permanent display at the Executive Offices in Chicago where flags of many nations represent College Chapters throughout the world. Drs. Maximo Carrizo Villarreal and Rodolfo V. Young, Regent and Governor respectively for the Republic of Panama, and Dr. Rene Vargas, Governor for Nicaragua, represented their countries in the flag presentations.

Dr. Burgess L. Gordon, Philadelphia, incoming President of the College, addressed the Convocation assembly. His address appears on page 114 of this issue of the College journal.

The Annual Presidents' Banquet followed the Convocation, which was attended by 575 physicians and members of their families. Preceding the Banquet, there was a cocktail party sponsored by the Panray Corporation of New York City. Dr. Herman J. Moersch, Rochester, Minnesota, President of the College, presided at the Banquet and introduced the officials and guests seated at the head table.

Dr. H. Allan Novack, Boston, a member of the Committee on Prize Essay Awards, introduced the winners of the College Essay Contest for 1957 and presented their certificates of merit and cash awards. The winners of the first and second prizes, James T. Post of the University of California Medical School, San Francisco and Henry Buchwald of Columbia University College of Physicians and Surgeons, New York City, were present to receive their certificates and cash awards in the amount of $500.00 and $300.00 respectively. The third prize winner, Stephen A. Kieffer, of the University of Minnesota Medical School, Minneapolis, could not be present and his certificate and cash award of $200.00 were received by Dr. J. Arthur Myers, Minneapolis, Past-President of the College and Editor-in-Chief of the College journal, *Diseases of the Chest*.

JOINT MEETING, BOARD OF REGENTS AND BOARD OF GOVERNORS NEW YORK CITY, MAY 31, 1957

Foreground, Dr. Coleman B. Rabin, New York City, newly elected Governor for New York State, presenting report. Head table, left to right, Dr. Jo Ono, Tokyo, Regent for Japan; Dr. Andrew L. Banyai, Milwaukee, Past-President and chairman, Council on International Affairs; Dr. Edgar Mayer, New York City, Regent, and chairman, General Arrangements Committee, 23rd Annual Meeting; Dr. David H. Waterman, Knoxville, chairman, Board of Governors, presiding; Dr. Donald R. McKay, Buffalo, President-Elect; Dr. John F. Briggs, St. Paul, chairman, Board of Regents; Mr. Murray Kornfeld, Chicago, Executive Director; and Dr. Burgess L. Gordon, Philadelphia, President.

Members of the Board of Regents and Board of Governors in annual session.

The presentation of the 1957 College Medal to Dr. William H. Feldman, of the Mayo Foundation, Rochester, Minnesota, was made by Dr. H. Corwin Hinshaw of San Francisco, formerly a member of the staff of the Mayo Foundation and co-worker with Dr. Feldman for many years. A photograph and brief biography of Dr. Feldman, who was selected the recipient of the Medal for his meritorious achievements in diseases of the chest, appear on pages 110-111 of this issue.

The Immediate Past President of the College, Dr. James H. Stygall, Indianapolis, presented to Dr. Moersch the Presidential Scroll of the College and the Past-President's Pin to Mrs. Moersch.

The international scope of the American College of Chest Physicians was emphasized by the presence of officials, members and guests from a number of countries, including Argentina, Australia, Brazil, Canada, Colombia, Costa Rica, Cuba, Denmark, Ecuador, England, France, Germany, India, Israel, Italy, Japan, Korea, Mexico, the Netherlands, Nicaragua, Panama, Peru, Philippine Islands, Poland, Puerto Rico, Sweden, Thailand, Turkey and Uruguay. Dr. Jo Ono, Regent for the College in Japan and Secretary-General of the Fifth International Congress on Diseases of the Chest to be held in Tokyo, September 7-11, 1958, attended the meeting and was introduced at the banquet. On behalf of his colleagues in Japan, he extended a cordial invitation to all members of the College to visit his country and assured them that a warm welcome would await those attending the Congress in 1958. Two Japanese girls, in native costume, distributing gifts from Japan, added a touch of the Orient. The College appreciates the courtesy extended by the airlines—Japan, Pan American and Northwest Orient, for making these gifts available.

A dance, sponsored by the New York Chapter of the College, completed the evening.

ADMINISTRATIVE MEETINGS

The Executive Council, Board of Regents and Board of Governors held a number of meetings in New York City where matters of policy were discussed and reports were received from the various councils and committees of the College. The proceedings of these meetings and the reports of councils and committees will be published in subsequent issues of the College journal.

On Saturday morning, June 1, the Open Administrative Session was held and reports were presented by the Historian, the Treasurer, the Committee on Bylaws, the Executive Director and the Committee on Nominations. The following officers, Regents and Governors were elected:

Officers

President:	Burgess L. Gordon, Philadelphia, Pennsylvania
President-Elect:	Donald R. McKay, Buffalo, New York
1st Vice-President:	Seymour M. Farber, San Francisco, California
2nd Vice-President:	M. Jay Flipse, Miami, Florida
Treasurer:	Charles K. Petter, Waukegan, Illinois
Assistant Treasurer:	Albert H. Andrews, Chicago, Illinois
Chairman, Board of Regents:	John F. Briggs, St. Paul, Minnesota

Regents

District No. 3:	Irving Willner, Newark, New Jersey
District No. 5:	Arnold S. Anderson, St. Petersburg, Florida
District No. 7:	Otto L. Bettag, Chicago, Illinois
District No. 9:	Hollis E. Johnson, Nashville, Tennessee
District No. 11:	Carl H. Gellenthien, Valmora, New Mexico
District No. 12:	George R. Herrmann, Galveston, Texas
District No. 13:	Elmer C. Rigby, Los Angeles, California
District No. 15:	Jaime F. Pou, Hato Rey, Puerto Rico
District No. 16:	Hastings D. Walker, Honolulu, Hawaii
Historian:	Carl C. Aven, Atlanta, Georgia

One of the scientific sessions at the 23rd Annual Meeting, Hotel Commodore, New York City. Simultaneous sessions on cardiovascular and pulmonary diseases were held; all sessions were well attended.

Governors

Alabama:	Paul W. Auston, Langdale
California:	Buford H. Wardrip, San Jose
Connecticut:	Arnold B. Rilance, New Haven
Florida:	Alexander Libow, Miami Beach
Georgia:	Osler A. Abbott, Emory University
Illinois:	Darrell H. Trumpe, Springfield
Louisiana:	Lawrence H. Strug, New Orleans
Michigan:	Winthrop N. Davey, Ann Arbor
Minnesota:	Sumner S. Cohen, Oak Terrace
Mississippi:	Robert E. Schwartz, Hattiesburg
Missouri:	Charles A. Brasher, Mt. Vernon
New Jersey:	Juan R. Herradora, Jersey City
New York:	Coleman B. Rabin, New York City
Tennessee:	David H. Waterman, Knoxville (Chairman)
Texas:	Henry R. Hoskins, San Antonio
Utah:	William Ray Rumel, Salt Lake City
Wyoming:	Herrick J. Aldrich, Sheridan

The following officers who had been serving as Temporary Regent and Temporary Governor for the Republic of Panama, were elected to office until the next international elections to be held in Tokyo, Japan, September, 1958:

Regent:	Maximo Carrizo Villarreal, Colon
Governor:	Rodolfo V. Young, Ancon

It was announced that the 24th Annual Meeting of the American College of Chest Physicians would be held at the Fairmont Hotel, San Francisco, California, June 18-22, 1958. All members of the College planning to attend the next annual meeting are urgently advised to make their hotel reservations well in advance. It is suggested that several choices of hotels be given in order that accommodations may be assigned in the vicinity of the Fairmont Hotel, in the event that accommodations are not available at the headquarters hotel. The Mark Hopkins and the Huntington Hotels are located nearby the Fairmont Hotel and are highly recommended. All requests for hotel reservations must be directed to the San Francisco Convention and Visitors Bureau, San Francisco 2, California, and it is advisable that mention be made of the American College of Chest Physicians meeting.

Announcement was also made that the Interim Session of the College would be held at the Warwick Hotel, Philadelphia, Pennsylvania, on December 2, 1957. The Clinical Meeting of the American Medical Association will be held in Philadelphia, December 3-6, 1957.

The Fifth International Congress on Diseases of the Chest, sponsored by the Council on International Affairs, American College of Chest Physicians, will be held in Tokyo, Japan, September 7-11, 1958. Information concerning the scientific program and transportation plans may be obtained by writing to the Executive Offices of the College in Chicago.

SCIENTIFIC PROGRAM

In planning the 23rd Annual Meeting of the College, the Committee on Scientific Program made certain changes and additions in both the form and content of the program as compared to previous years. The marked increase in membership of the College, and the steadily broadening of interest in the different fields of chest diseases, seemed to require a more diversified program which would appeal to the various interests of those attending. More emphasis was placed on papers dealing with original basic research work. Since more than 100 abstracts were submitted, with an abundance of excellent material, it was decided to have two sessions on basic research running concurrently. This same plan of holding concurrent sessions was followed in the other areas of the program in order to provide time for the many excellent papers submitted. The large attendance at all of the different sessions certainly confirmed the need for this plan.

FELLOWS OF THE COLLEGE RECEIVE GOLD MEDALS FOR EXHIBITS PRESENTED AT THE AMERICAN MEDICAL ASSOCIATION MEETING IN NEW YORK CITY

(Photo at left): The Hektoen gold medal was presented to Drs. C. Walton Lillehei, H. E. Warden, R. A. DeWall, Vincent L. Gott, R. D. Sellers, M. Cohen, R. C. Read, Richard L. Varco and O. H. Wangensteen, Minneapolis, for their exhibit "The Direct (Open) Surgical Repair of Congenital and Acquired Intracardia Malformations." Dr. Gott (left) is pictured explaining part of its apparatus to Dr. Melvin Wein of Brooklyn. Drs. Lillehei and Varco are Fellows of the American College of Chest Physicians.

(Photo at right): The Biliings gold medal was awarded to Drs. Robert G. Trout, Robert P. Glover and J. C. Davila, Philadelphia, for their exhibit "The Present Indications for Cardiac Surgery." Dr. Trout (left) is discussing the exhibit with Dr. Joseph Summer. Dr. Glover is a Fellow of the American College of Chest Physicians.

The Clinical X-ray Conference was, as always, one of the highlights of the meeting. The EKG panel was held for the first time this year and the large attendance at this, in addition to the session on clinical cardiology, and the symposium and panel on congenital cardiology, provided ample evidence of the rapidly increasing interest of the members in these fields. The extremely well-attended symposia on pulmonary function, tuberculosis, and nuclear energy, indicated the great interest in these fields. As in previous years, the Fireside Conferences and the round table luncheon panels were enthusiastically received.

The Scientific Program Committee is most grateful to the many members of the College for their ideas and suggestions. The Committee for the 1958 meeting is already hard at work making plans and will welcome any comments or suggestions. Members who wish to submit papers for possible presentation at the annual meeting of the College in San Francisco, June 18-22, 1958, are invited to write directly to the chairmen of the program committee, as follows, accompanied by an abstract of the material they wish to present.

Dr. Samuel Bellet, 2021 Spruce Street, Philadelphia
Chairman, Section on Cardiovascular Diseases

Dr. Peter A. Theodos, 1930 Chestnut Street, Philadelphia
Chairman, Section on Pulmonary Diseases

LADIES ACTIVITIES

A delightful program was arranged for the ladies attending the 23rd Annual Meeting. Mrs. Alfred S. Dooneief, Chairman, with the enthusiastic cooperation of the members of her committee, planned a special activity for each day of the meeting. On Thursday, May 30, a luncheon was held at the Waldorf-Astoria Hotel where the Arthur Murray Dancers performed for the ladies and gave them lessons in the "Cha-Cha." On Friday evening, May 31, one hundred "lucky ladies" had the opportunity of seeing "My Fair Lady," currently the most popular Broadway musical, while their husbands attended the Fireside Conferences, the most popular feature of the annual College meetings. A breakfast party was held at the Charleston Garden Restaurant of B. Altman & Company on Saturday morning, June 1, and in the evening the ladies attended the Annual Convocation, Cocktail Party and Presidents' Banquet of the College held at the Hotel Commodore. The Ladies Reception Committee arranged a calendar of events for Sunday, June 2, which included visits to museums, concerts, art exhibits, etc. In addition, tickets for popular television shows were available during the days of the meeting.

SECTION ON DISEASES OF THE CHEST AMERICAN MEDICAL ASSOCIATION

Certificate of Merit was awarded to Drs. Edwin R. Levine and Abel Froman, Chicago Medical School and Edgewater Hospital, Chicago, for the exhibit on "Bronchial Drainage: Physiologic and Mechanical Aids to Bronchial Evacuation" shown at the annual meeting of the American Medical Association in New York City, June 3-7.

Drs. John W. Irwin, Irving H. Itkin, Sandylee Weille and Nancy Little, Massachusetts General Hospital, Boston, were given Honorable Mention for the exhibit on "Bronchial Asthma."

Honorable Mention was also given to the exhibit on "Lung Cancer and Smoking: Relationship and Changes in the Bronchial Epithelium" by Drs. Oscar Auerbach, J. Brewster Gere, Harold J. Smolin, Jerome R. Forman, Gerald E. Muehsam, Joseph M. Pawlowski and Arthur Purdy Stout, Veterans Administration Hospital, East Orange, New Jersey.

Obituary

HAROLD GUYON TRIMBLE
1896-1957

Leaders in the fields of medicine, health, research, civic enterprise, and hosts of friends and patients mourn the tragic death on May 13th of Dr. Harold Guyon Trimble. He was a member of the Board of Regents of the American College of Chest Physicians and an internationally famed chest specialist.

Dr. Trimble was born in Oakland, California on February 27, 1896 and graduated from the University of California Medical School in 1920. His early interest in chest diseases stemmed from association with Drs. Robert Peers and George Evans. His vigorous life and medical practice have resulted in outstanding accomplishments and honors.

He was a Diplomate of the American Board of Internal Medicine and an Associate Clinical Professor of Medicine, Stanford University School of Medicine. He was a Fellow of the American College of Physicians, the American College of Chest Physicians, American Public Health Association and the American Geriatrics Society. He was a member of the California Academy of Medicine and the California Society of Internal Medicine.

In 1941-1942, Dr. Trimble was President of the American Trudeau Society, and in 1943-1944 was Vice-President of the National Tuberculosis Association. In 1941, he served as President of the California Tuberculosis and Health Association.

He gained world renown in the field of chest disease through his many trips abroad to lecture in this field and on May 14, 1954, he was the recipient of the Fourth Sir Pendrill Varrier-Jones Memorial Medal, Manson House, London. Such trips took him throughout Europe, South America, and the Far East.

He was also the recipient of the 1957 Annual Medal of the California Tuberculosis and Health Association (for Meritorious Service in the Tuberculosis Campaign). These are but a few of his many appointments and honors which indicate the extent of his contribution and service to his profession.

Dr. Trimble's activities and interests were not confined to his profession. He took an active part in community and religious affairs and served on the Board of Directors of the United Crusade, The Salvation Army, Boys Club of Oakland and Bay Area Citizens' Committee for the World Health Association.

Dr. Trimble had great affection for his family of which he was justly proud. He leaves his widow Esther, five children and thirteen grandchildren. His passing will be deeply felt. He will be remembered by his associates not only for his wonderful personality and as a staunch and devoted friend, but also as a great physician and a leader in the fight to overcome tuberculosis and other diseases of the chest.

Buford H. Wardrip, M.D.
Governor for California

MEDICAL SERVICE BUREAU

Staff physician wanted, full time, for 270-bed chest disease hospital, approved for residency training in pulmonary diseases. Located in Murphys, California. Starting salary $700 per month, plus home on grounds, furnished. Available July 1, 1957. Must have California license. Apply: Superintendent, Bret Harte Sanatorium, Murphys, California.

Staff physician wanted for 215-bed hospital for chronic pulmonary diseases. Salary commensurate with qualifications and experience. Living quarters and laundry are provided. Must be a graduate of an approved school. Contact E. W. Hainlen, M.D., Director of Medical Services, Emily P. Bissell Sanatorium, 3000 Newport Gap Pike, Wilmington 8, Delaware.

Physician wanted. Immediate opening for director of 40-bed tuberculosis ward in 450-bed G. M. & S. hospital affiliated with two medical schools. Excellent teaching opportunities and research facilities available. Apply Dr. K. W. Brown, Director, Professional Services, Veterans Administration Hospital, 4101 Woolworth Avenue, Omaha, Nebraska.

Director, diagnostic and research tuberculosis laboratory, wanted in central Florida. Physician or non-physician microbiologist or clinical chemist. Part-time employment considered. Write: Dr. Albert V. Hardy, Director, Bureau of Laboratories, State Board of Health, PO Box 210, Jacksonville, Florida.

Physician wanted for 324-bed tuberculosis hospital, 88 miles south of Cleveland, treating all phases of chest diseases and many interesting general medical diseases. Experience not necessary. Salary up to $13,760, depending upon experience and qualifications. U. S. citizen, preferably under 54. Apply to Manager, Veterans Administration Hospital, Brecksville, Ohio.

Tuberculosis physician wanted. Salary $968 to $1176 per month. Letter of acceptance to board eligibility in internal medicine, plus at least one year residency in chest diseases required. Apply Riverside County Personnel Department, Court House, Riverside, California.

Staff physician experienced in tuberculosis needed. Must be graduate Grade A U. S. medical school or Canadian medical school for state license. Large sanatorium with over 1,000 patients in daily census. Active medical and surgical programs. Please address inquiries to Box 291A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

Interim Session and Semi-Annual Meeting, Board of Regents
American College of Chest Physicians
Philadelphia, December 2, 1957

24th Annual Meeting, American College of Chest Physicians
Fairmont Hotel, San Francisco, June 18-22, 1958

Fifth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Tokyo, Japan, September 7-11, 1958

POSTGRADUATE COURSES

12th Annual Postgraduate Course on Diseases of the Chest
Hotel Knickerbocker, Chicago, October 21-25

10th Annual Postgraduate Course on Diseases of the Chest
Park-Sheraton Hotel, New York City, November 11-15

3rd Annual Postgraduate Course on Diseases of the Chest
Ambassador Hotel, Los Angeles, December 9-13

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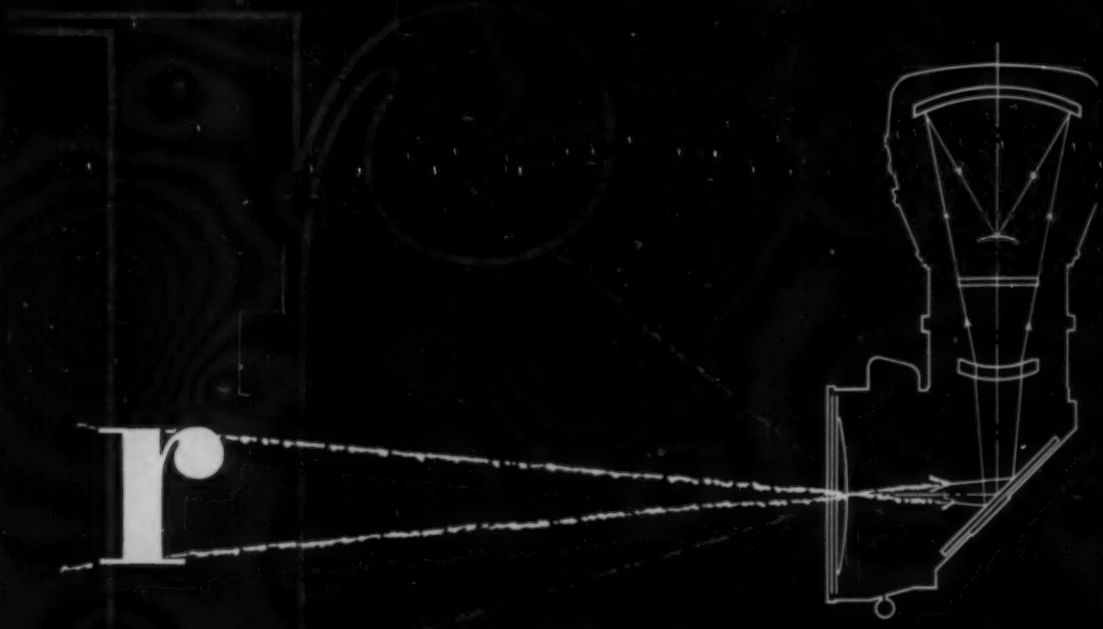

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At the same time, resolution is more than doubled —which insures sharp, crisp negatives of diagnostic quality. The resolution of this system exceeds that of the fluorescent screen. The camera's speed also stops much voluntary and involuntary motion, virtually eliminating retakes.

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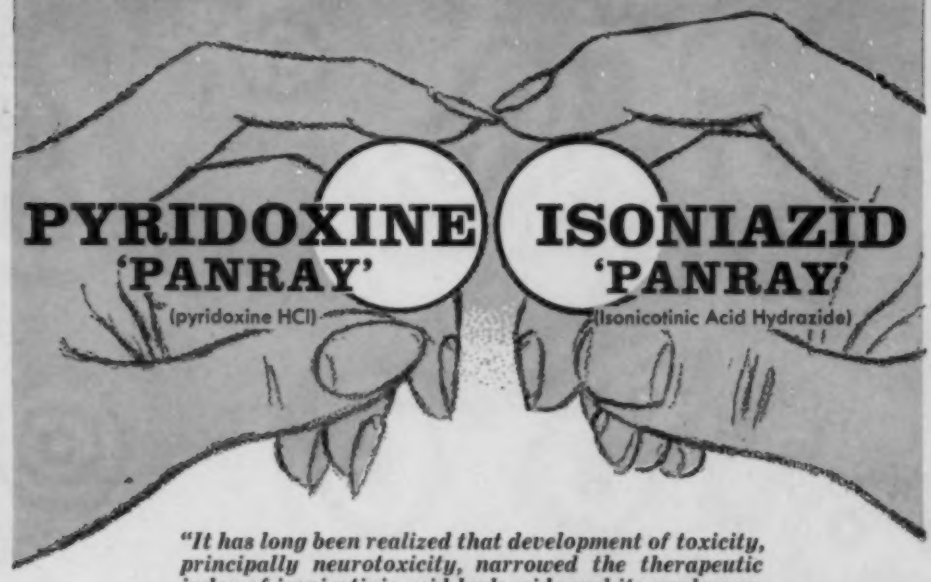
HAND IN HAND

in the Chemotherapy of Tuberculosis



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[1]Sea View Bulletin 16:62 July '56 Tchertkoff, et al. JAMA 156:1549 (Dec. 25) 1954 Biehl & Viltner Am. Rev. TBc 70:266 Aug. '54 Hughes, et al. N. Eng. J. of Med. 255 #3 118-122, 1956 Carlson, et al.